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British Journal of Anaesthesia



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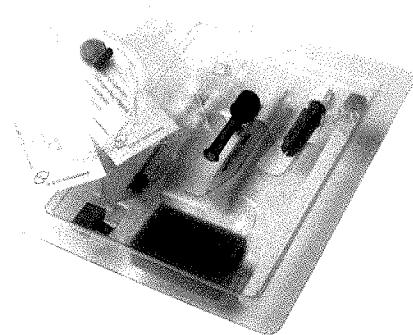


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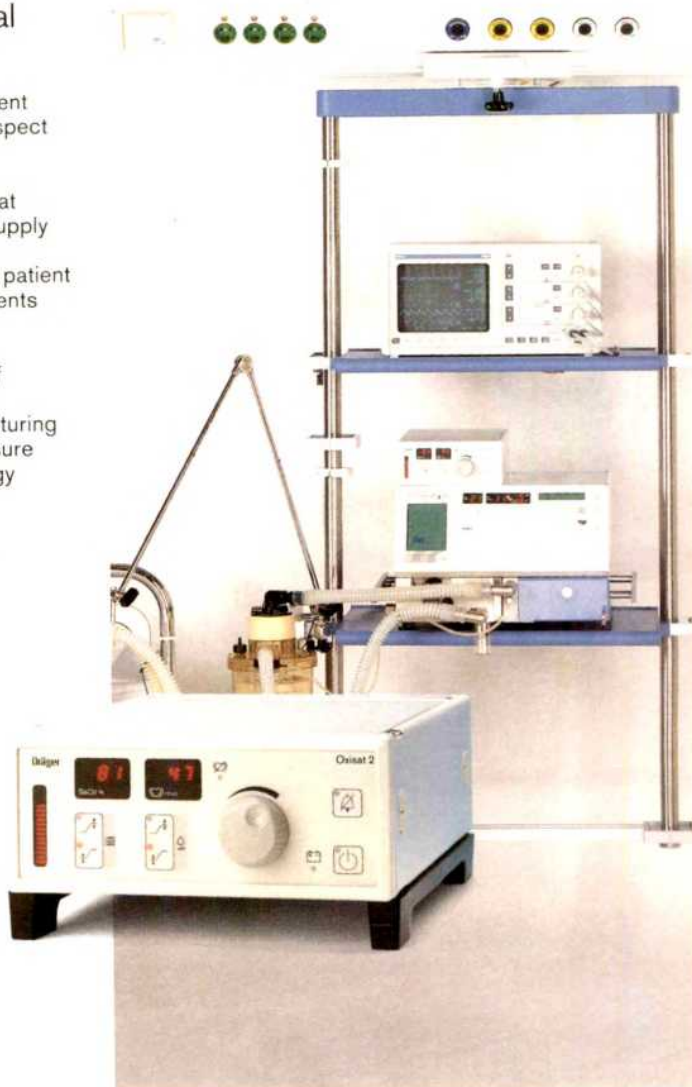
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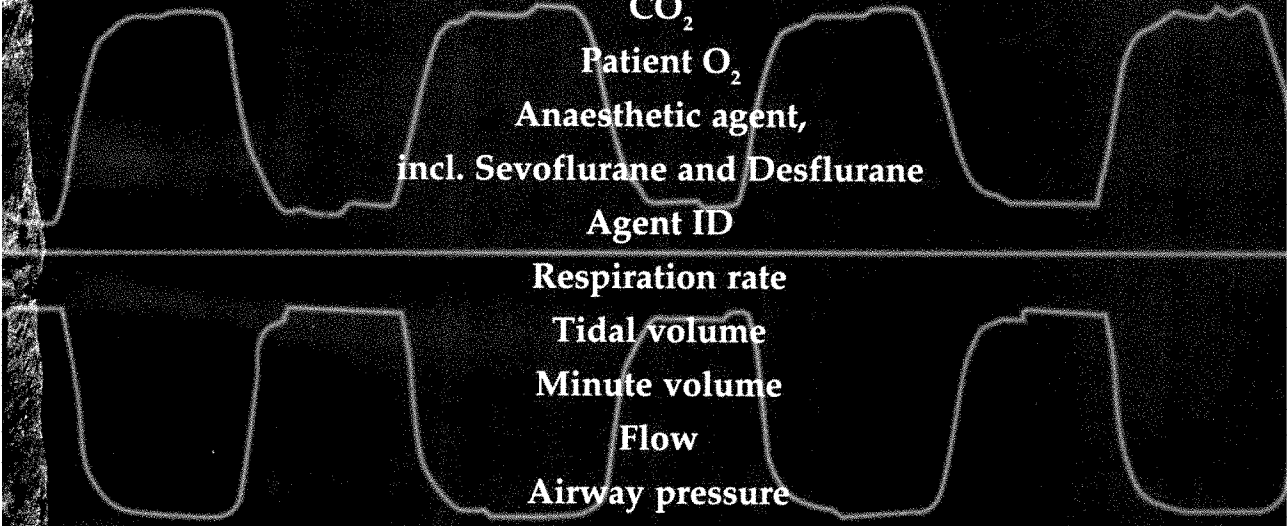
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- Summary
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- Methods
- Results
- Discussion
- Acknowledgements
- List of references
- Tables
- Illustrations

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There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

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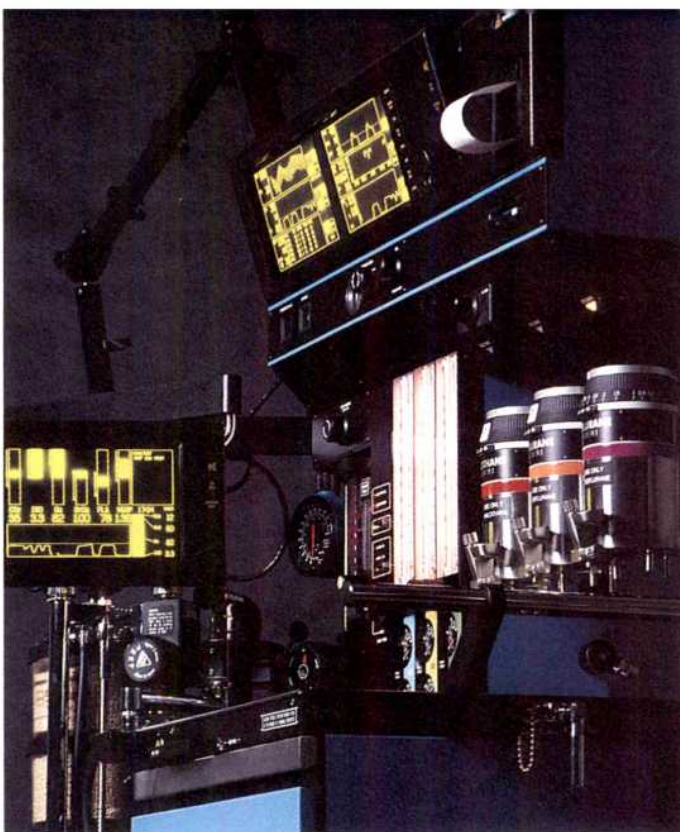
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(Hemodynamic and hemorrhagic reactions
after tumor implantation)

A. Schöler, R.F. Meier, W. Meier
W. Furlen, Th. J. Lohse
Beurteilung der kardiopulmonalen
und der hämodynamischen
Reaktion bei Tumorblutungen
(Evaluation of the cardiopulmonary and
hemodynamic reaction in tumor bleeding)

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Originalien

Hämodynamische Parameter zur Abschätzung des myokardialen Sauerstoffverbrauchs in der Anaesthetie

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Hemodynamic variables reflecting myocardial
oxygen consumption in anaesthesia

Abstract. Direct measurements of myocardial oxygen consumption (MO_2) and of a number of hemodynamic variables were performed in 60 patients with coronary heart disease undergoing three-vessel coronary artery bypass surgery. Anaesthetic procedures included halothane, enflurane, isoflurane, propofol, fentanyl, midazolam, fentanyl, and morphine anaesthesia. The following hemodynamic variables were correlated with MO_2 : heart rate (HR), cardiac index (CI), stroke volume index (SVI) and arithmetic combined variables $P_{\text{mean}} \times HR$, $P_{\text{mean}} \times CI$, $P_{\text{mean}} \times SVI$, $P_{\text{mean}} \times HR \times CI$, $P_{\text{mean}} \times HR \times SVI$, $P_{\text{mean}} \times HR \times CI \times SVI$.

The product of $P_{\text{mean}} \times (HR)$ is equivalent to the tension time index as modified by Bretschneider and the index of Sarnoff as modified by Robinson. Production and uptake of lactate as metabolic equivalents of myocardial oxygen consumption. Measurements were performed with the patients awake, after induction of anaesthesia without surgical stimulation, during sternotomy and after the operation. We observed 20% evaluable mean hemodynamic variables that correlated best with MO_2 was systolic pressure ($r = 0.67$). Stroke volume index ($r = 0.31$) and heart rate ($r = 0.32$) were poorly correlated. The combined hemodynamic variables that correlated most closely with MO_2 were the tension time index modified by Bretschneider ($P_{\text{mean}} \times (HR)$) and Robinson ($P_{\text{mean}} \times HR \times CI$) ($r = 0.75$). Production and consumption of lactate were not correlated with myocardial oxygen consumption. There was a difference in the correlation between MO_2 and variables as opposed to intravenous anaesthesia. These results indicate that MO_2 cannot be estimated from systolic blood pressure and heart rate alone. There are no safe limits for blood pressure, heart rate and rate pressure.

product that exclude myocardial ischemia. Because of regional differences in the myocardial oxygen consumption, it cannot be detected solely from arterial-luminal differences. It is not advisable to assume 'safe limits' of hemodynamic variables, rather, individual monitoring is mandatory during anaesthesia and operation. Adequate close monitoring of blood pressure, heart rate and ECG may help to detect myocardial ischemia.

Zusammenfassung. An 60 Patienten mit koronärer Herzkrankheit, die sich einer koronaren Bypass-Operation unterzogen, wurden direkte myokardiale Sauerstoffverbräuche (MO_2) und eine Reihe von hämodynamischen Messungen unter dem Einfluss folgender Anaesthetika: Halothan, Enfluran, Isofluran, Propofol, Fentanyl, Midazolam, Fentanyl und Morphin. Folgende hämodynamische Parameter wurden mit dem myokardialen Sauerstoffverbrauch korreliert: maximale systolische Blutdruck (P_{max}), mittlerer arterieller Blutdruck (MAP), Herzfrequenz (HR), Herzindex (CI) und Schlagvolumenindex (SVI). Aus den Einzelparametern wurden durch Multiplikation folgende Kombinationsparameter gebildet, die ebenfalls mit dem direkten myokardialen Sauerstoffverbrauch korreliert wurden: $P_{\text{mean}} \times HR$, $P_{\text{mean}} \times CI$, $P_{\text{mean}} \times SVI$, $P_{\text{mean}} \times HR \times CI$, $P_{\text{mean}} \times HR \times SVI$, $P_{\text{mean}} \times HR \times CI \times SVI$.

Das Produkt $P_{\text{mean}} \times (HR)$ entspricht dem modifizierten Tension-Time-Index nach Bretschneider, das Produkt $P_{\text{mean}} \times HR \times CI$ nach Robinson.

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EDITORIAL I

SILENT MYOCARDIAL ISCHAEMIA IN PREOPERATIVE PATIENTS: WHAT DOES IT MEAN, AND WHAT SHOULD BE DONE ABOUT IT?

The very first issue of the *Lancet* described a man who died suddenly during ligation of a femoral artery aneurysm (under an oral brandy anaesthetic). Why do patients die from ischaemic heart disease during and after surgery? Sudden arrhythmic cardiac death is a common "out of hospital" form of death in patients with coronary artery disease, but skilful anaesthesia and cardiac monitoring have made it an uncommon event perioperatively. Coronary thrombosis is still a problem: we now know from angiographic studies following thrombolysis and from experience during angioplasty that an atheromatous plaque which previously caused no significant coronary obstruction (and thus no symptoms) may crack and precipitate occlusive thrombosis over a time course of a few hours. The third type of perioperative collapse occurs in patients with severe three-vessel coronary disease or left mainstem obstruction who are subjected to transient hypotension or hypoxaemia: there is a sudden reduction in cardiac output causing further hypotension, increased ischaemia, and a "vicious circle" which can be difficult or impossible to break. The main objectives of preoperative cardiac assessment are to identify patients at high risk of perioperative infarction, and to identify patients who already have such extensive coronary disease that their ability to cope with circulatory instability is limited.

The Oxford group [1] have detected silent myocardial ischaemia by preoperative continuous ECG monitoring in 7.2% of a male "general surgical" population and 18.6% of male patients about to undergo vascular surgery. This has to be set in the context of previous population studies which have shown high prevalences of *some* manifestation of coronary artery disease in a substantial number of randomly selected middle aged to elderly males. Rose, using a carefully validated questionnaire, found evidence of anginal

symptoms in approximately 4% of middle aged males [2]. Shaper and colleagues [3] found resting ECG criteria of definite or possible ischaemic heart disease in 15% of a group of 7735 men aged between 40 and 59 yr identified at random from general practice records. The mechanism of silent myocardial ischaemia in ambulant outpatients seems to be identical to that of "painful" ischaemia, or angina: the temporary inadequacy of myocardial blood supply as a consequence of a fixed stenosis in a coronary artery. Overt and "silent" ischaemia commonly coexist, and are suppressed in parallel by agents such as beta-adrenoceptor antagonists [4]. In patients with known ischaemic heart disease, the presence of silent ischaemia is an independent predictor of the risk of death or infarction [5], but the prognostic significance of silent ischaemia in unselected outpatients is not yet known, and is likely to be less. Both the mechanism and significance of silent ischaemia in the context of recent unstable angina, angioplasty or thrombolytic treatment for coronary thrombosis are different: here the likely cause is an unstable thrombus overlying cracked or denuded endothelium, and silent ischaemia is a good marker for subsequent coronary occlusion [6].

Until we know more about the prognostic significance of silent ischaemia in asymptomatic patients with good exercise tolerance it would be premature to use continuous ECG monitoring as a preoperative screening test for non-vascular patients, other than in the context of a prospective, randomized trial. Such a trial would need to be very large, because the expected number of endpoints would be small; moreover, the problem of false positive ST changes becomes important in a low risk population [7].

The situation is different in patients with peripheral vascular disease, in that angiographic studies have shown a prevalence of coronary

artery disease in these patients which approaches 100%, and the peri- and postoperative cardiovascular morbidity rates are much greater. The question is not if coronary artery disease exists, but whether it is severe enough to make surgery inadvisable, or to alter anaesthetic practice. Patients with peripheral vascular disease are also likely to have their mobility handicapped to an extent which makes assessment of angina by exercise testing impracticable. In this group, continuous ECG monitoring and assessment of left ventricular function by radioisotope ventriculography (*not* echocardiography, which can be unreliable in patients with localized ventricular dysfunction) can be very useful components of preoperative assessment. Patients with frequent or severe episodes of ischaemia, or in whom ischaemia is impossible to assess because of pre-existing ECG changes, can be assessed further by dipyridamole/thallium scanning, coronary angiography (using a brachial approach if the iliac vessels are compromised), or both. Which particular assessment technique is chosen will depend on local resources; the important point is that there should be a well-planned and standardized cardiac assessment routine. The tempo of investigation will obviously vary with the urgency of the case.

Final decisions require close collaboration between anaesthetist, surgeon and cardiologist. Patients with severe stenosis of the left main coronary artery, or with severe proximal three-vessel disease, should be considered in the first instance for coronary bypass grafting [8]. We are currently performing palliative coronary angioplasty for some patients with severe proximal coronary stenosis, but its safety and efficacy have yet to be evaluated fully. In theory at least, the disrupted endothelium produced by angioplasty could act as a focus for postoperative thrombosis. Increased plasma concentrations of fibrinogen have been shown to be a marker for

thrombosis risk, and postoperative anticoagulation may be appropriate [9]. Patients with diffuse coronary disease or well established coronary collateral circulations often do well without cardiological interference. Cardiac disease is the commonest cause of death in patients with vascular disease, and heroic vascular surgery in patients with severe and irremediable cardiac problems may not be appropriate.

D. P. de Bono and E. L. Rose

REFERENCES

1. Muir AD, Reeder MK, Fox P, Ormerod OJM, Sear JW, Johnston C. Preoperative silent myocardial ischaemia: incidence and prediction in a general surgical population. *British Journal of Anaesthesia* 1991; 67: 373-377.
2. Rose G. Variability of angina. Some implications for epidemiology. *British Journal of Preventive Social Medicine* 1968; 22: 12-15.
3. Shaper AG, Cook DG, Walker M, Macfarlane PW. Prevalence of ischaemic heart disease in middle aged British Men. *British Heart Journal* 1984; 51: 595-605.
4. Carboni GP, Lahiri A, Cashman PMN, Raftery EB. Ambulatory heart rate and ST-segment depression during painful and silent myocardial ischemia in chronic stable angina pectoris. *American Journal of Cardiology* 1987; 59: 1029-1034.
5. Deedwania PC, Carbajal EV. Silent ischaemia during daily life is an independent predictor of mortality in stable angina. *Circulation* 1990; 81: 748-756.
6. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcome in patients with unstable angina. *New England Journal of Medicine* 1986; 314: 1214-1219.
7. Kohli RS, Cashman PMM, Lahiri A, Raftery EB. The ST segment of the ambulatory electrocardiogram in a normal population. *British Heart Journal* 1988; 60: 4-16.
8. ACC/AHA Task Force Report. Guidelines and indications for coronary artery bypass surgery. *Journal of the American College of Cardiologists* 1991; 17: 543-589.
9. Kannell WB, D'Agostino A, Belanger AJ. Fibrinogen, cigarette smoking and risk of cardiovascular disease: insights from the Framingham Study. *American Heart Journal* 1987; 113: 1006-1010.

EDITORIAL II

DRUG BIOTRANSFORMATION BY THE KIDNEY: HOW IMPORTANT IS IT, AND HOW MUCH DO WE REALLY KNOW?

For most i.v. agents, the liver plays the pivotal role in drug elimination—conversion of lipophilic active drugs to hydrophilic, polar inactive metabolites that may be eliminated via the kidney.

Most studies investigating the handling of drugs by the body are based on discrete plasma drug sampling regimens to provide a concentration–time profile, from which the researcher may determine systemic clearance either from the derivation of a polyexponential equation describing the concentration–time relationship, or by use of statistical moment analysis (based on calculation of the “area under the curve” (AUC) and its first moment (AUMC)).

Both of these approaches have advantages and difficulties. One problem is delineation of the site of drug clearance. Studies depend usually upon peripheral blood sampling (ideally arterial, although often venous), and so ignore any influence that the lung might have as an organ of drug extraction, metabolism, or both. The latter function has been reviewed recently in this journal by Bakhle [1], while sequestration (and later release of drug back into the systemic circulation) has been observed for drugs such as fentanyl, alfentanil and pethidine [2–4], although not for morphine [2, 5].

If we ignore the lung (or ascertain that it plays little role in drug clearance), the anaesthetist may assume he can equate systemic drug clearance with hepatic clearance. However, the enzymes responsible for drug metabolism (by both the microsomal mixed function oxygenase (MFO) and UDPG transferase pathways, and the extra-microsomal pathways of acetylation, methylation and sulphate and mercapturic acid conjugation) exist in many other tissues of the body [6, 7], including gastrointestinal epithelial cells, vascular epithelial cells, brain and kidney. If we express hepatic MFO activity as 100%, the activity in the lung is approximately 2%, but that in the kidney is 10–20%. If drug metabolism occurs in sites in addition to the liver, we may find situations where clearance rates in excess of liver blood flow might occur [8, 9].

It is important to remember, however, that

the main causes of high clearance rates are poor sampling regimens (too short to delineate adequately the terminal half-life), limited assay sensitivity (leading to underestimates of half-life and the accompanying overestimate of clearance), or poor data handling.

Another method of investigating the contributions of different drug metabolic sites has been the application of flux experiments: determining organ blood flow and inflow–outflow concentration gradient, and hence calculating the amount of drug cleared by the organ per unit time [10].

Most of the enzymes needed for MFO-mediated drug metabolism and the UDPG transferase are present in the renal cortex and are present in greatest activities in the S_1 and S_3 cells of the proximal tubules. Many estimates of renal enzyme activity have been made using renal homogenates or slices, and hence the overall determination of activity may underestimate that in the S_2 and S_3 cells. Several studies have reported the activities of enzymes (such as N-acetyl transferase using para-aminobenzoic acid as the substrate) to have kidney:liver ratios of > 0.94 in the mouse and > 1.0 in rabbit and guinea pig [11]. Among those drugs of interest to the anaesthetist, which undergo *in vitro* metabolism in the renal parenchyma, are paracetamol, sulindac, para-aminobenzoic acid, salicylates, morphine, pethidine and isoproterenol [12–17].

What of morphine and the opioids *in vivo*? Analysis of urinary morphine concentrations after parenteral administration has revealed that only 1–2% of drug is eliminated unchanged [18, 19]. The main metabolites are morphine-3- and 6-glucuronides, and normorphine, with smaller amounts of the diglucuronide and 3-ethereal sulphate, and normorphine-6-glucuronide. From our data following i.v. administration of morphine to anaesthetized patients [20] and other data from man [21, 22], the biotransformation of morphine to the 3-glucuronide is greater than to the 6-glucuronide (unless there is preferential excretion of the latter by the kidneys). The ratios of AUC_{0-24h} (M3G:M6G) are in the range 5–10:1.

In an elaborate set of experiments aimed at

defining the contribution of different organs to the clearance of morphine, Sloan and colleagues [23] have turned to their well-established model of the chronically cannulated Merino sheep (although reservations must be held concerning the total extrapolation of the data to the human subject!). To determine systemic clearance of morphine, they have used the relationship between input rate and pulmonary artery morphine concentration at steady state. Renal clearance was determined as the product of renal blood flow (measured using PAH) and the renal arterial-venous difference. Systemic clearance rates for morphine vary considerably between studies in man, dogs and goats [24–28]. As noted by Sloan and colleagues, some of the estimates clearly exceed what is normally equated with hepatic blood flow.

In the present studies by Sloan and co-workers [23], the estimated renal clearance exceeded the amount of drug found in the urine; and the authors correctly surmised that loss of drug (i.e. metabolism) must have occurred in the renal parenchyma. The mean value of 35% for renal metabolism in this study compares well with the results from Jacqz and colleagues [29] in the dog, and the recent data from Mazoit and colleagues [19], who found a 33% non-urinary, non-hepatic metabolism of morphine in man. Thus renal metabolism appears to make a significant contribution to total biotransformation of morphine, and as such offers a possible explanation for the absence of any reduction in systemic clearance of morphine in patients with cirrhosis [30–32], and the extrahepatic metabolism of the opioid during the anhepatic phase of patients undergoing orthotopic liver transplantation [33].

Based on the data of Schali and Roch-Ramel [13], the apparent K_m for metabolism of morphine by the kidney is about 700 nmol litre⁻¹; increased rates for morphine metabolism therefore may be achieved by the kidney within the therapeutic concentration ranges if liver metabolism is impaired.

What of the synthetic opioids used commonly during anaesthesia? Studies examining the disposition of fentanyl, alfentanil and sufentanil show no significant decreases in systemic clearance in patients with advanced renal disease treated by dialysis [34–42]. The main metabolic pathways in man are N-dealkylation, O-demethylation and aromatic hydroxylation, with the renal excretion of less than 4–6% of fentanyl, 5–10% of sufentanil and < 1% of alfentanil [43–47].

There are few studies comparable to the present one on regional clearance fluxes, although Schedewie and colleagues [48] have measured directly the hepatic clearance of sufentanil in anaesthetized subjects. Further studies are indicated, especially in the light of the wide variability in clearance estimates for all three drugs in healthy subjects. Clearance estimates based on regional blood flows and organ extraction ratios may allow the anaesthetist to answer several questions: what are the metabolic contributions of the various body organs, and what are the likely influences of drug therapy or disease states on systemic opioid handling?

It should be self evident that direct extrapolation from animal data to man may be confusing. There is much evidence that renal failure is associated with impaired drug metabolism in animal models, while the possibility of the contrary enhancement of hepatic drug metabolism has been suggested in man [49].

J. W. Sear

REFERENCES

1. Bakhle YS. Pharmacokinetic and metabolic properties of lung. *British Journal of Anaesthesia* 1990; 65: 79–93.
2. Roerig DL, Kotrly KJ, Vucins EJ, Ahif SB, Dawson CA, Kampine JP. First pass uptake of fentanyl, meperidine and morphine in the human lung. *Anesthesiology* 1987; 67: 466–472.
3. Roerig DL, Kotrly KJ, Ahif SB, Dawson CA, Kampine JP. Effect of propranolol on the first pass uptake of fentanyl in human and rat lung. *Anesthesiology* 1989; 71: 62–68.
4. Taeger K, Weninger E, Schmelzer F, Adt M, Francke N, Peter K. Pulmonary kinetics of fentanyl and alfentanil in surgical patients. *British Journal of Anaesthesia* 1988; 61: 425–434.
5. Ratcliffe FM. Absence of morphine glucuronidation in the human lung. *European Journal of Clinical Pharmacology* 1989; 37: 537–538.
6. Mather LE, Runciman WB, Ilsley AH, Thomson KR, Goldin AR. Direct measurement of chlormethiazole extraction by liver, lung and kidney in man. *British Journal of Clinical Pharmacology* 1981; 12: 319–325.
7. Pacifici GM, Bencini C, Rane A. Presystemic glucuronidation of morphine in humans and rhesus monkeys: subcellular distribution of the UDP-glucuronyltransferase in the liver and intestine. *Xenobiotica* 1986; 16: 123–128.
8. Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ. Disposition of propofol in patients undergoing surgery. A comparison in men and women. *British Journal of Anaesthesia* 1986; 58: 1075–1079.
9. Lange H, Stephan H, Rieke H, Kellermann M, Sonntag H, Bircher J. Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery. *British Journal of Anaesthesia* 1990; 64: 563–570.

10. Upton RN, Mather LE, Runciman WB, Nancarrow C, Carapetis RJ. The use of mass balance principles to describe regional drug distribution and elimination. *Journal of Pharmacokinetics and Biopharmaceutics* 1988; 16: 13-29.
11. Litterst CL, Mimnaugh EG, Reagan RL, Gram TE. Comparison of *in vitro* drug metabolism by lung, liver and kidney of several common laboratory species. *Drug Metabolism and Disposition* 1975; 3: 259-265.
12. Ross B, Tange J, Emslie K, Hart S, Smail M, Calder I. Paracetamol metabolism by the isolated perfused rat kidney. *Kidney International* 1980; 18: 562-570.
13. Schali C, Roch-Ramel F. Transport and metabolism of [³H] morphine in isolated, nonperfused proximal tubular segments of the rabbit kidney. *Journal of Pharmacology and Experimental Therapeutics* 1982; 223: 811-815.
14. Miller MJS, Bednar MM, McGiff JC. Renal metabolism of sulindac: Functional implications. *Journal of Pharmacology and Experimental Therapeutics* 1984; 231: 449-456.
15. Wan SH, von Lehmann B, Riegelman S. Renal contribution to overall metabolism of drugs. III: Metabolism of para-aminobenzoic acid. *Journal of Pharmaceutical Sciences* 1972; 61: 1288-1292.
16. Bekersky I. Use of the isolated perfused kidney as a tool in drug disposition studies. *Drug Metabolism Reviews* 1983; 14: 931-960.
17. Szeffler SJ, Acara M. Isoproterenol excretion and metabolism in the isolated perfused rat kidney. *Journal of Pharmacology and Experimental Therapeutics* 1979; 210: 295-300.
18. Yeh SY, Gorodetzky CW, Krebs HA. Isolation and identification of morphine 3- and 6-glucuronides, morphine 3,6-diglucuronide, morphine 3-etheral sulfate, normorphine, normorphine 6-glucuronide as morphine metabolites in humans. *Journal of Pharmaceutical Sciences* 1977; 66: 1288-1293.
19. Mazoit JX, Sandouk P, Scherrmann J-M, Roche A. Extrahepatic metabolism of morphine occurs in humans. *Clinical Pharmacology and Therapeutics* 1990; 48: 613-618.
20. Sear JW, Hand CW, Moore RA, McQuay HJ. Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites. *British Journal of Anaesthesia* 1989; 62: 28-32.
21. Osborne R, Joel S, Trew D, Slevin M. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine 6-glucuronide. *Clinical Pharmacology and Therapeutics* 1990; 47: 12-19.
22. Sawe J, Odar-Cederlof I. Kinetics of morphine in patients with renal failure. *European Journal of Clinical Pharmacology* 1987; 32: 377-382.
23. Sloan PA, Mather LE, McLean CF, Rutten AJ, Nation RL, Milne RW, Runciman WB, Somogyi AA. Physiological disposition of i.v. morphine in sheep. *British Journal of Anaesthesia* 1991; 67: 378-386.
24. Stanski DR, Paalzow L, Edlund PO. Morphine pharmacokinetics: GLC assay versus radioimmunoassay. *Journal of Pharmaceutical Sciences* 1982; 71: 314-317.
25. Aitkenhead AR, Vater M, Achola K, Cooper CMS, Smith G. Pharmacokinetics of single-dose i.v. morphine in normal volunteers and patients with end-stage renal failure. *British Journal of Anaesthesia* 1984; 56: 813-818.
26. Andersen HB, Christensen B, Findlay JWA, Jansen JA. Pharmacokinetics of intravenous, intrathecal and epidural morphine and fentanyl in the goat. *Acta Anaesthesiologica Scandinavica* 1986; 30: 393-399.
27. Chauvin M, Sandouk P, Scherrmann JM, Farinotti R, Strumza P, Duvaldestin P. Morphine pharmacokinetics in renal failure. *Anesthesiology* 1987; 66: 327-331.
28. Sear JW, Hand CW, Moore RA, McQuay HJ. Studies on morphine disposition: influence of general anaesthesia on plasma concentrations of morphine and its metabolites. *British Journal of Anaesthesia* 1989; 62: 22-27.
29. Jacqz E, Ward S, Johnson R, Schenker S, Gerken J, Branch RA. Extrahepatic glucuronidation of morphine in the dog. *Drug Metabolism and Disposition* 1986; 14: 627-630.
30. Patwardhan RV, Johnson RF, Hoyumpa A, Sheehan JJ, Desmond PV, Wilkinson GR, Branch RA, Schenker S. Normal metabolism of morphine in cirrhosis. *Gastroenterology* 1981; 81: 1006-1011.
31. Crotty B, Watson KJR, Desmond PV, Mashford ML, Wood LJ, Colman J, Dudley FJ. Hepatic extraction of morphine is impaired in cirrhosis. *European Journal of Clinical Pharmacology* 1989; 36: 501-506.
32. Mazoit JX, Sandouk P, Zetlaoui P, Scherrmann JM. Pharmacokinetics of unchanged morphine in normal and cirrhotic subjects. *Anesthesia and Analgesia* 1987; 66: 293-298.
33. Bodenham A, Quinn K, Park GR. Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation. *British Journal of Anaesthesia* 1989; 63: 380-384.
34. Corall IM, Moore AR, Strunin L. Plasma concentrations of fentanyl in normal surgical patients, and those with severe renal and hepatic disease. *British Journal of Anaesthesia* 1980; 52: 101P.
35. Gulden D, Koehntop D, Rodman J, Brundage D, Hegland M. Fentanyl pharmacokinetics during renal transplantation. *Anesthesiology* 1984; 61: A243.
36. Van Peer A, Vercauteren M, Noordijn H, Woestenborghs R, Heykants J. Alfentanil kinetics in renal insufficiency. *European Journal of Clinical Pharmacology* 1986; 30: 245-247.
37. Chauvin M, Lebrault C, Levron JC, Duvaldestin P. Pharmacokinetics of alfentanil in chronic renal failure. *Anesthesia and Analgesia* 1987; 66: 53-56.
38. Bower S, Sear JW. Disposition of alfentanil in patients receiving a renal transplant. *Journal of Pharmacy and Pharmacology* 1989 41: 654-657.
39. Sear JW. Disposition of fentanyl and alfentanil in patients undergoing renal transplantation. In: Bergmann H, Steinbereither K, eds. VII European Congress of Anaesthesiology. Proceedings I (Main topics 1-6). *Beitrage zur Anasthesiologie und Intensivmedizin* 1987; 19: 53-58.
40. Sear JW. Sufentanil disposition in patients undergoing renal transplantation: influence of choice of kinetic model. *British Journal of Anaesthesia* 1989; 63: 60-67.
41. Fyman PN, Reynolds JS, Moser F, Avitabile M, Casthely PA, Butt K. Pharmacokinetics of sufentanil in patients undergoing renal transplantation. *Canadian Journal of Anaesthesia* 1988; 35: 312-315.
42. Davis PJ, Stiller RL, Cook DR, Brandon BW, Davin-Robinson KA. Pharmacokinetics of sufentanil in adolescent patients with chronic renal failure. *Anesthesia and Analgesia* 1988; 67: 268-271.

43. McClain Da, Hug CC jr. Intravenous fentanyl kinetics. *Clinical Pharmacology and Therapeutics* 1980; 28: 106-114.
44. Bovill JG, Sebel PS. Pharmacokinetics of high-dose fentanyl. *British Journal of Anaesthesia* 1980; 52: 795-801.
45. Goromaru T, Matsuura H, Yoshimura N, Miyawaki T, Sameshima T, Miyao J, Furuta T, Baba S. Identification and quantitative determination of fentanyl metabolites in patients by gas chromatography-mass spectrometry. *Anesthesiology* 1984; 61: 73-77.
46. Schuttler J, Stoeckel H. Alfentanil (R 39209): Ein neues kurzwirkendes opioid. *Anaesthesist* 1982; 31: 10-14.
47. Meuldermans W, Van Peer A, Hendrickx J, Woestenborghs R, Lauwers W, Heykants J, Vanden Bussche G, Van Craeyvelt H, Van Der Aa P. Alfentanil pharmacokinetics and metabolism in humans. *Anesthesiology* 1988; 69: 527-534.
48. Schedewie HK, Lee LA, Cowan GS, Gold RE, Bottorff MB, Peters TG, Heerdt ME, Angel JJ. Hepatic clearance of sufentanil in humans. *Anesthesiology* 1987; 67: A291.
49. Balant LP, Dayer P, Fabre J. Consequences of renal insufficiency on the hepatic clearance of some drugs. *International Journal of Clinical Pharmacological Research* 1983; 3: 459-474.

PREOPERATIVE SILENT MYOCARDIAL ISCHAEMIA: INCIDENCE AND PREDICTORS IN A GENERAL SURGICAL POPULATION

A. D. MUIR, M. K. REEDER, P. FOËX, O. J. M. ORMEROD, J. W. SEAR AND C. JOHNSTON

SUMMARY

We have studied before operation 156 patients aged more than 40 yr presenting for elective vascular or non-vascular surgery, using ambulatory ECG monitoring to detect silent myocardial ischaemia (SMI). The prevalence of SMI was 18.2% in the vascular group (n = 102) and 7.6% in the non-vascular group (n = 54). A history of ischaemic heart disease, or an abnormal ECG suggestive of a previous myocardial infarction, predicted a high risk of SMI (28% compared with 9% in the absence of these variables). However, a significant amount of SMI (36% of the total) occurred in patients without one of the defined risk factors. In addition, 24 of the patients with abdominal aortic disease underwent cardiac gated blood pool (MUGA) scans. Abnormal ventricular wall function was observed in 62.5% of the patients. Twenty-nine percent of the patients studied with MUGA scans had SMI and 21% had ejection fractions < 40%. A significant association ($P < 0.05$) existed between the presence of SMI and a ventricular ejection fraction of < 40%.

KEY WORDS

Heart: silent myocardial ischaemia. Measurement techniques: MUGA scan. Surgery: preoperative period.

Patients presenting for peripheral vascular surgery are at increased risk of postoperative cardiac complications compared with the general surgical population [1], as a result of an increased incidence of coronary heart disease [2]. Preoperative assessment of cardiac risk is based on a history of cardiac limitation which may be masked by vascular symptoms. Thus vascular surgery patients failing to give a history of exertional

angina or dyspnoea may have severe, clinically unrecognizable ischaemic heart disease (IHD). Conventional exercise tests may be unhelpful as these patients may fail to achieve levels of exertion needed to produce adequate cardiovascular stress.

Ambulatory ECG monitoring is a reliable method of detecting ST segment depression reflecting myocardial ischaemia [3, 4]. Much of the ischaemia has been found to be "silent", occurring often at normal heart rates [5]. This suggests that the predominant mechanism is decreased myocardial oxygen supply rather than increased oxygen demand [6], although the exact aetiology of silent ischaemia is at present uncertain.

Fox [7] noted, in patients with known IHD, that silent ischaemic episodes were twice as common as those accompanied by pain, and had identical accompanying pathophysiological changes. Others have found that persistent ST-segment abnormalities after ischaemic pain was eliminated were independent predictors of cardiac morbidity and mortality [8, 9]. Furthermore, the prognosis of patients with IHD correlates with the total amount of ischaemia as opposed to the amount of symptomatic ischaemia [4, 8, 10].

In view of the recent interest in preoperative silent ischaemia [9, 11], the aim of our study was to determine the prevalence of silent myocardial ischaemia (SMI) in vascular and non-vascular

This article is accompanied by Editorial I.

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surgical populations, using ambulatory ECG monitoring and to identify patient characteristics that might predispose towards SMI.

PATIENTS AND METHODS

One hundred and fifty-six consecutive patients older than 40 yr gave informed verbal consent to the study. Patients were excluded if they had ECG abnormalities precluding interpretation of the ST segment, namely: left bundle branch block; left ventricular hypertrophy with strain pattern; marked ST/T wave changes associated with digoxin therapy; signal-to-noise ratio preventing meaningful interpretation.

TABLE I. Variables entered into the stepwise logistic regression analysis and criteria for a positive value

Variable	Type	Characteristics
Ischaemic heart disease	Logical	Presence of either angina (exertional chest pain or pain radiating in a cardiac distribution, relieved by rest) or past MI.
ECG	Logical	ECG evidence suggesting presence of a past MI not predicted from patient's history.
Hypertension	Logical	Currently treated hypertension or persistent diastolic AP > 100 mm Hg after admission.
Occlusion	Logical	Symptoms of occlusive vascular disease (i.e. history of claudication).
Age	Integer	Number of decades.
Weight group	Integer	Number of times 10% greater than ideal body weight.
Obesity	Logical	Is patient > 20% greater than ideal body weight?
Positive family	Logical	MI at age less than 60 yr. History in an immediate family member.
Diabetes	Logical	Presence/absence of diabetes mellitus.
Smoking	Logical	Smoking more/less than 20 pack-day years. (One pack-day year equals one pack per day for 1 year, or equivalent.)
Silent myocardial ischaemia	Logical	Presence/absence SMI.
Arrhythmias	Logical	Presence/absence of more than one ventricular ectopic beat min ⁻¹ throughout the whole study.

Patients agreeing to participate had detailed cardiac histories taken and were examined by one of the investigators. Cardiac risk factors, past medical history, clinical examination and basic laboratory investigations were recorded, as were the presence or absence of 10 variables (less ECG evidence of SMI or arrhythmias) (table I). Solid state ambulatory ECG monitors (Medilog 6000 FD or Kontron micro FD) were attached to the patient on the day before operation and removed the following morning, before induction of anaesthesia. Electrodes were placed to record an inferior lead (lead 2) and a lateral chest lead (V5). A purpose-designed computer with inbuilt ECG interpretation software was used to analyse the recordings. Any reported ST segment changes were checked by a human observer. During the study period, patients were ambulatory in the hospital ward and underwent routine preoperative assessment.

An ST segment depression was considered significant if a planar or downsloping ST segment depression equal to or greater than 1 mm persisting 80 ms after the J point and lasting for more than 1 min was present. Each episode was terminated by a return to baseline ≥ 1 min.

A subset of 24 patients presenting for aortic reconstructive surgery was studied before operation with a cardiac gated blood pool scan (equilibrium radionuclide ventriculography or MUGA scan). Left ventricular function was assessed by ejection fraction and regional wall motion by single harmonic Fourier phase and amplitude images. Views were obtained at rest and during exercise.

Statistical analysis

The association between preoperative variables and the presence or absence of SMI was determined using stepwise logistic regression (Glim programme, Numerical Algorithms Group Ltd, Oxford). Within the different surgical subgroups, comparison of the incidence of SMI was made using chi-square test with Yates' correction.

Data are shown as mean (SD).

RESULTS

We studied 156 patients, 102 from vascular and 54 from non-vascular surgical wards, for a mean duration of 16.7 h (range 8–24 h). Thirty patients had a previous proven myocardial infarction (MI). Twenty-one patients were suffering from angina

TABLE II. Age (mean (range)) and prevalence of SMI in the two patient study groups

	Vascular (n = 102)	Non-vascular (n = 54)	Statistical significance
Age (yr)	65.2 (46-83)	59.8 (40-79)	$P < 0.01$
SMI			
Present	19 (18.6%)	6 (11.1%)	$\chi^2 = 2.16$
Absent	83 (81.4%)	48 (88.9%)	$P > 0.05$

and 56 patients had treated hypertension or a diastolic pressure > 100 mm Hg on at least three separate recordings after admission. Forty patients were receiving drug therapy for treatment of angina, hypertension or both (21 β -blockers; 15 calcium channel blockers; four both drugs). No patient commenced therapy after admission.

Occurrence of SMI and relationship to risk factors

Patient ages and the prevalence of SMI in the two groups are shown in table II.

Stepwise logistic regression of the 11 dependent variables indicated that the only variables contributing significantly to a model describing the prevalence of SMI were pre-existing IHD or abnormal preoperative ECG suggesting a previous MI not predicted from the patient's history. The combination of both selected variables occurred in only five patients, three of whom had SMI. This gives cell sizes of 3 and 2 for people positive for both predictors. Because of the small size of these patient groups, and therefore of the potential errors when incorporating them into a derived logistic model, we combined the two variables as a single factor (b in the equation below).

The probability for the absence of SMI is given by:

$$p(\text{absence of SMI}) = \frac{e^{-1.6218 + b0.6808}}{1 + e^{-1.6218 + b0.6808}}$$

where p = probability of no SMI; b = a history of IHD or abnormal ECG (as defined in table I); e = natural logarithm.

As there was no difference in the prevalence of SMI between patients undergoing vascular and non-vascular surgery (chi-square test), we subjected the whole study population to the model and determined the predicted prevalences of SMI in the patient subgroups (table III).

TABLE III. Predicted and observed prevalences of SMI in patient subgroups

	ECG normal no IHD	ECG abnormal or IHD
Predicted incidence of SMI (%)	9.09	28.07
SE of predicted probability (%)	2.89	5.95
Observed number with SMI	9	16
Observed number without SMI	90	41

The observed prevalence of SMI approximated closely to those predicted. Twenty-five of 156 patients were positive for SMI; nine of these (36%) were outside the high risk group as identified by the stepwise regression analysis. Medication with adrenoceptor blockers or with calcium channel blockers did not affect the occurrence of SMI (chi-square test, $P > 0.05$).

Relationship of SMI to myocardial function

MUGA revealed myocardial abnormalities in 62.5% of the patients. Five of the 24 patients (20.8%) had a ventricular ejection fraction $< 40\%$. The overall incidence of SMI was 29.2% ($n = 7$) with 57% of these patients ($n = 4$) having ejection fractions $< 40\%$. There was a significant association between an ejection fraction $< 40\%$ and SMI ($P < 0.05$). Eighty percent of the patients with a reduced ejection fraction had evidence of SMI, compared with only 16% in the patients with ejection fractions $> 40\%$. There was no significant association between a past history of MI and ejection fraction $< 40\%$.

DISCUSSION

Our study has indicated that silent myocardial ischaemia was a relatively common preoperative event in both vascular and non-vascular surgical patients aged more than 40 yr. The overall incidence (15%) is in general agreement with those reported elsewhere in similar patient populations [9, 10, 12-21].

The inability to demonstrate a significant difference in the prevalence of SMI between patients undergoing vascular and non-vascular surgery is probably a reflection of the sample size and the heterogeneous nature of the populations. The non-vascular sample included patients with

substantial degrees of occlusive arterial disease, admitted for non-vascular surgical procedures.

The only useful predictors of SMI are those direct indicators of the presence of current or past IHD; none of the other selected cardiovascular risk factors, such as positive family history, peripheral vascular occlusive symptoms and male sex, had any direct influence. Any effect these variables were having on the model was exerted via their status as risk factors for IHD. The results are in accord with those of Raby [9] that indices of past or present myocardial disease are the most significant.

Whilst the presence of proven IHD predicts a high risk of SMI (28%), 36% of the total SMI observed was in patients without evidence of IHD. Thus, if it were considered clinically important to detect SMI, all patients should be studied.

As in other studies [12], we have demonstrated a strong association between impaired left ventricular function and SMI. Patients with poor ventricular function are at risk from myocardial ischaemia which may further depress function, increasing the risk of postoperative cardiac complications. A clinical history of angina or previous MI failed to predict significantly the likelihood of a poor ejection fraction, as not all episodes of MI cause significant reduction in myocardial function, and some remain clinically silent or undiagnosed. Objective assessment of left ventricular function may be valuable in patients before major surgery [11, 22, 23].

A large, prospective study has demonstrated a high frequency of SMI in vascular surgical patients before operation and found that postoperative cardiac morbidity was confined almost exclusively to those with preoperative SMI [9]. A 24-h ambulatory ECG study free of SMI may thus indicate that the patient is at low risk of postoperative cardiac complications. In view of the relationship between SMI and poor ejection fraction, detection of SMI before operation should, in the authors' view, lead to investigation of cardiovascular function including either an echocardiogram or a radionuclide study.

As episodic ST depression may be missed on a single 24-h recording, a negative study must be interpreted with caution and its value as an acceptable preoperative screening test remains unclear. It should not replace the present methods of assessing cardiovascular risk, such as echocardiography or radionuclide imaging.

ST segment depression may occur in normal healthy individuals [24], unrelated to myocardial ischaemia. Fox [7] stated that, in volunteers, they occur with tachycardia and are rarely greater than 2 mm. The majority occur at night and are thought to be positional. It is possible that some of the reported prevalence of ST segment depression (and, by inference, SMI) is unrelated to the presence of myocardial ischaemia. The exact criteria for a significant ST segment change are unclear, but there is good evidence that the criteria used in this paper reflect myocardial ischaemia [3, 4, 25-28].

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REFERENCES

1. Jamieson WR, Janusz MT, Miyagishima RT, Gerein AN. Influence of ischemic heart disease on early and late mortality after surgery for peripheral occlusive vascular disease. *Circulation* 1982; 66 (Suppl. I): I92-I97.
2. Hertzner NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF, Graor RA, De Wolfe VG, Maljovec LC. Coronary artery disease in peripheral vascular disease: classification of 1000 coronary angiograms and results of surgical management. *Annals of Surgery* 1984; 199: 223-233.
3. Leppo J, Plaja J, Gionet M, Tumulo J, Paraskos JA, Cutler BS. Noninvasive evaluation of cardiac risk index before elective vascular surgery. *Journal of the American College of Cardiology* 1987; 9: 269-276.
4. Cohn PF. Silent myocardial ischemia: classification, prevalence, and prognosis. *American Journal of Medicine* 1985; 79 (Suppl. 3A): 2-6.
5. Deanfield JE, Maseri A, Selwyn AP, Ribeiro P, Chierchia S, Krickler S, Morgan M. Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. *Lancet* 1983; 2: 753-758.
6. Kowalchuk GJ, Nesto RW. Silent myocardial ischemia. Mechanisms and rationale for therapy. *American Journal of Medicine* 1989; 86: 9-12.
7. Fox KM. Should we treat silent ischaemia? *Journal of Cardiovascular Pharmacology* 1987; 10 (Suppl. 2): S34-S36.
8. Gottlieb SO, Weisfelt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia predicts infarction and death in a 2 year follow up of unstable angina. *Journal of the American College of Cardiology* 1987; 10: 756-760.
9. Raby KE, Goldman L, Creager MA, Cook SE, Weisberg MC, Whittemore AD, Selwyn AP. Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. *New England Journal of Medicine* 1989; 321: 1296-1300.

10. Nademanee K, Intrachot V, Josephson MA, Reiders D, Mody FV, Singh BN. Prognostic significance of silent myocardial ischemia in patients with unstable angina. *Journal of the American College of Cardiology* 1987; 10: 1-10.
11. Pasternack PF, Grossi EA, Baumann FG, Riles TS, Lamparello PJ, Giangola G, Primis LK, Mintzer R, Imparato AM. The value of silent myocardial ischemia monitoring in the prediction of perioperative myocardial infarction in patients undergoing peripheral vascular surgery. *Journal of Vascular Surgery* 1989; 10: 617-625.
12. Gottlieb SO, Weisfelt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent myocardial ischemia as a marker for early unfavorable outcomes in patients with unstable angina. *New England Journal of Medicine* 1986; 314: 1214-1219.
13. Tzivoni D, Gavish A, Benhorin J, Keren A, Stern S. Myocardial ischemia during daily activities and stress. *American Journal of Cardiology* 1986; 58: 47B-50B.
14. Carboni GP, Lahiri A, Cashman PM, Raftery EB. Ambulatory heart rate and ST-segment depression during painful and silent myocardial ischemia in chronic, stable angina pectoris. *American Journal of Cardiology* 1987; 59: 1029-1034.
15. Theroux P, Waters DD, Halphen C, Debaisieux JC, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *New England Journal of Medicine* 1979; 301: 341-345.
16. Erikssen J, Thaulow E. Follow-up of patients with asymptomatic myocardial ischaemia. In: Rutishauser W, Roskamm H, eds. *Silent Myocardial Ischaemia*. Berlin: Springer-Verlag, 1984: 156-164.
17. Langou RA, Huang EK, Kelley MJ, Cohen LS. Predictive accuracy of coronary artery calcification and abnormal exercise test for coronary artery disease in asymptomatic men. *Circulation* 1980; 62: 1196-1203.
18. Knight AA, Hollenberg M, London MJ, Tubau J, Verrier E, Browner W, Mangano DT. Preoperative myocardial ischemia: are anesthesia and surgery truly stressful to the ischemic heart? *Anesthesiology* 1987; 67: A592.
19. Fegert G, Hollenberg M, Browner W, Wellington MS, Levenson L, Franks M, Harris D, Mangano DT. Perioperative myocardial ischemia in the noncardiac surgical patient. *Anesthesiology* 1988; 69: A49.
20. Wilton NTC, Luckoff C, Sachdev M, Kirsh M, Shea M. Silent preoperative myocardial ischemia in surgical patients with ischemic heart disease. *Anesthesiology* 1987; 67: A591.
21. Lutsch P, Heijke S, Rowbotham D. Preoperative ST abnormalities detected by the Compass ambulatory ECG monitor in patients scheduled for peripheral arterial surgery. *British Journal of Anaesthesia* 1990; 65: 272P.
22. Pasternack PF, Imparato AM, Bear G. The value of radionuclide angiography as a predictor of perioperative myocardial infarction in patients undergoing abdominal aortic aneurysm repair. *Journal of Vascular Surgery* 1984; 1: 320-325.
23. Pasternack PF, Imparato AM, Riles TS. The value of the radionuclide angiogram in the prediction of perioperative myocardial infarction in patients undergoing lower extremity revascularization procedures. *Circulation* 1985; 72 (Suppl. II): II13-II17.
24. Quyyumi AA, Wright C, Fox K. Ambulatory electrocardiographic ST changes in healthy volunteers. *British Heart Journal* 1983; 50: 460-464.
25. Berman DS, Rozanski A, Knoebel SB. The detection of silent ischaemia: cautions and precautions. *Circulation* 1987; 75: 101-105.
26. Selwyn AP. The value of Holter monitoring in managing patients with coronary artery disease. *Circulation* 1987; 75 (Suppl. II): 31-32.
27. Rotman B, Eber B, Duslag J, Fluch N, Weinrauch V, Klein W. Comparison of different methods of ST measurement for evaluation of myocardial ischaemia in Holter monitoring. *European Heart Journal* 1988; 9 (Suppl. N.): 78-84.
28. Kennedy HL. Ambulatory electrocardiography strategies used in assessing silent myocardial ischaemia. *European Heart Journal* 1988; 9 (Suppl. N.): 70-77.

PHYSIOLOGICAL DISPOSITION OF I.V. MORPHINE IN SHEEP†

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SUMMARY

In a crossover design study we have measured the total body and regional clearances of morphine. Thirteen experiments were performed in four conscious sheep that had been prepared previously with appropriate intravascular cannulae. Morphine (as sulphate pentahydrate) was infused i.v. at 2.5, 5, 10 and 20 mg h⁻¹ to produce constant blood concentrations. Morphine (base) concentrations were measured in blood, urine and tissues with a specific HPLC method. The mean (SEM) total body clearance of morphine was 1.63 (0.21) litre min⁻¹; this comprised 1.01 (0.10) litre min⁻¹ clearance by the liver and 0.55 (0.06) litre min⁻¹ by the kidneys. There was no evidence of dose-dependent clearance or significant extraction of morphine by the lungs, brain, heart, gut or hindquarters at any dose. The kidney clearance of morphine was greater than the 0.21 (0.06) litre min⁻¹ renal clearance determined from the product of the mean total body clearance and the 12.3 (2.4)% of the administered dose recovered as unmetabolized morphine from 48 h urine collection (P < 0.05). It was concluded that the liver and kidneys account for the majority of morphine clearance, and that the kidneys both excrete and metabolize morphine.

KEY WORDS

Analgesics: morphine. Kidney, drug metabolism: morphine. Liver, drug metabolism: morphine. Pharmacokinetics: morphine, regional clearance.

liver is the primary organ for elimination of morphine from the body. Biotransformation of morphine by conjugation with glucuronic acid, producing morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), is known to comprise the principal metabolic pathway before excretion of these metabolites into urine [2]. However, over the past 6 years, the role of the kidney in morphine clearance has been the subject of much contention. The early report of a decreased rate of morphine elimination in renal transplant patients that drew attention to this association [3] is now considered inaccurate because of unintentional simultaneous measurement in plasma of both morphine and M6G [4]. Nevertheless, there is indirect evidence of extrahepatic clearance of morphine. In some human pharmacokinetic studies, it has been found that morphine total body clearance may approach or even exceed the putative liver blood flow [5-8]. This is supported by observation of the similarity in morphine clearances in healthy subjects and in patients with hepatic cirrhosis [9]. Moreover, it is

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The physiological disposition of morphine is poorly understood, despite its long history and widespread clinical use. As little morphine is excreted unmetabolized into urine (approximately 10% of the dose [1]) it has been taught that the

known that human kidney microsomes [10] are capable of metabolizing morphine to M3G and M6G, although the relevance of this finding to the disposition of morphine *in vivo* is not clear.

In most reports to date, the pharmacokinetics of morphine have been determined from peripheral or central venous plasma concentrations. This method of pharmacokinetic analysis, however, does not permit simultaneous investigation of the involvement of individual body regions. To examine the involvement of individual regions in the clearance of morphine, we carried out experiments in sheep with multiple intravascular cannulae so that the systemic and regional clearances could be determined simultaneously.

MATERIALS AND METHODS

Experimental design

Approval was given by the institutional Ethics Review Committee for this study to be performed in sheep prepared previously with chronic intravascular catheters to enable drug infusion, cardiovascular monitoring and regional blood sampling for blood flow indicator and morphine analyses. From these data, the systemic and regional clearances of morphine were measured. Adult merino ewes of mean (SD) weight 48 (8) kg were studied.

Animal preparation

The general methods and materials used for animal preparation have been described in detail in previous publications from this laboratory [11, 12]; the methods specific to the present study are described here briefly. Under general anaesthesia, a left-sided thoracotomy was performed to ligate the hemi-azygos vein which, in the sheep, contributes systemic venous blood to the coronary sinus. Intra-abdominal catheters were placed directly into the abdominal aorta (distal to the renal artery and proximal to the iliac bifurcation), mesenteric and portal veins via, respectively, left paravertebral and right subcostal skin incisions. After surgical exposure of the vessels in the neck, two arterial catheters were placed in the right carotid artery with their tips positioned approximately 2 cm above the aortic valve. Catheters were placed in the right jugular vein with their tips in the coronary sinus, left renal vein, posterior vena cava, right hepatic vein and right atrium (two catheters), and a flow directed thermodilution catheter was placed with its tip in

the pulmonary artery. An additional catheter was placed in the sagittal sinus via a frontal incision and a trephine hole in the parietal bone. At least 1 week was allowed for the sheep to recover from surgery before the first experiment was performed.

Blood flow measurements

Cardiac output was measured using the pulmonary artery thermodilution catheter after injection of ice cold 0.9% saline 10 ml into a right atrial catheter. Gut and hindquarter blood flows were measured by indicator dilution using infusion into the mesenteric vein and abdominal aorta, respectively, of the indicators sodium para-aminohippurate (PAH) and sodium bromosulphophthalein (BSP) [12]. Liver and kidney blood flows were measured at times similar to those for gut and hindquarter blood flow determinations by the Fick method using, respectively, BSP and PAH. Steady state blood concentrations of the indicators were achieved with two-stage infusions using a constant rate infusion pump with individually calibrated glass syringes: a 15-min loading dose of BSP 32 mg min^{-1} and PAH 8 mg min^{-1} was followed by maintenance infusions of BSP 16 mg min^{-1} and PAH 4 mg min^{-1} . After 45 min of maintenance infusions, simultaneous ascending aortic and appropriate regional venous blood sample sets (0.4 ml) were obtained at 15-min intervals for a further 60 min. Gut and hindquarter blood flows were calculated from the quotients, respectively, of the PAH and BSP maintenance dose rates and the appropriate venous-arterial concentration difference. Liver and kidney blood flows were calculated from the quotients, respectively, of the BSP and PAH maintenance dose rates and the appropriate arterial-regional venous concentration differences [12].

Morphine administration and sample collection

Two-stage infusions of morphine were made into a right atrial catheter: loading infusions of 8 times the maintenance rate were made over 15 min and maintenance doses of morphine (as sulphate pentahydrate) 2.5, 5, 10 and 20 mg h^{-1} were infused for 345 min. This regimen was determined from computer simulation from preliminary data obtained by right atrial infusion of morphine 10 mg/10 min in one animal. Traditional three-compartment open model analysis of the resultant arterial blood morphine concen-

tration-time data collected for 4 h indicated a mean total body clearance of $2.16 \text{ litre min}^{-1}$, a steady state volume of distribution of 86 litre and a slow half-life of 82 min. Four experiments, performed in random order at least 3 days apart at each of the four morphine infusion rates, were planned in each of four animals to assess the potential dose-dependence of total body and regional clearances of morphine but three experiments were not completed because of catheter failure.

The last 60 min of the morphine maintenance infusion was regarded as the "steady state" period. During this period, five sets of 1.0-ml blood samples were obtained simultaneously at 15-min intervals from the aortic, pulmonary artery, sagittal sinus, coronary sinus, hepatic, portal, renal and posterior vena cava catheters for measurement of blood concentrations of morphine, together with cardiac output and liver, kidney, gut and hindquarter blood flows by methods described above. Urine was collected from the start of morphine infusion by indwelling catheter from 0-6 h and from 6-24 and 24-48 h by free flow for measurement of morphine concentrations in eight experiments. In pilot studies, it had been shown that hydrolysis of morphine conjugates did not occur under the conditions of collection and storage.

Terminal experiments

The last experiment at each dose rate was a terminal experiment for the measurement of morphine tissue:blood partition coefficients. After completion of the blood sampling period, the animal was killed immediately with a bolus of saturated potassium chloride solution 30 ml, at which time the morphine infusion was stopped. Tissue samples were obtained within 10 min from the whole brain, lung, left ventricle, liver, small bowel, kidney, hindquarter muscle and fat for morphine analysis.

Morphine concentration analysis

Blood, urine and tissue samples were stored at -20°C until batch assay to measure morphine concentrations (as base) by normal phase high performance liquid chromatography (HPLC) after solvent extraction [13]. The method, which is selective for morphine, involves internal standardization with hydromorphone, selective pH extraction and elution followed by optimized electrochemical detection to provide high sen-

sitivity (to 0.5 ng ml^{-1}), linearity ($r^2 > 0.998$ from 5 to 500 ng ml^{-1}) and reproducibility (coefficients of variation, respectively, 2.4 and 2.7% for 20 and 200 ng ml^{-1} , $n = 15$ each).

Data analysis

The total body clearance (Cl) of morphine was obtained from the ratio of the maintenance infusion rate to the mean pulmonary artery blood concentration of morphine during the steady state period. Pulmonary arterial, rather than aortic, blood morphine concentrations were used in the calculation of Cl , as only this calculation remains correct should there be lung clearance. However, upon retrospective analysis, there was no systematic difference when Cl was calculated from aortic blood concentration of morphine ($P > 0.05$, Student's t test for paired data). The regional clearances of morphine were determined directly from the relevant products of the regional extraction ratios and regional blood flows [12]. In addition, the renal clearance of morphine was determined indirectly from the product of the mean total body clearance and the fraction of dose excreted by 48 h into urine. The results of the indicator dilution measurement of gut blood flow were considered to be unreliable because of apparent streaming of the PAH; gut blood flow was estimated therefore as 80% of liver blood flow [11, 14]. Brain and coronary blood flows were estimated, respectively, as 2% of cardiac output [14] and $1.09 \text{ ml min}^{-1}/\text{g}$ of sheep heart [15].

Morphine tissue:blood partition coefficients were determined at steady state from the terminal experiments using, for reference, the relevant mean arterial concentration during the steady state period. The calculated partition coefficient, $k_p = C_t/C_b$ (where C_t and C_b are the morphine concentrations in tissue and blood, respectively), assumes the lack of clearance from tissues [16]. For tissues in which clearance occurred, the partition coefficient was determined as $K_p = (1 + Cl_t/Q_t) \cdot C_t/C_b$ (where Cl_t is tissue clearance, and Q_t is tissue blood flow) [16]. The median partition coefficients were combined with the median blood flow and clearance data to simulate the time course of blood, liver, gut, kidney, muscle concentrations and urinary excretion of morphine [16].

The relationships between dose and morphine systemic and regional kinetics were examined using multiple regression by partitioning the dose effects into linear, quadratic and cubic trend

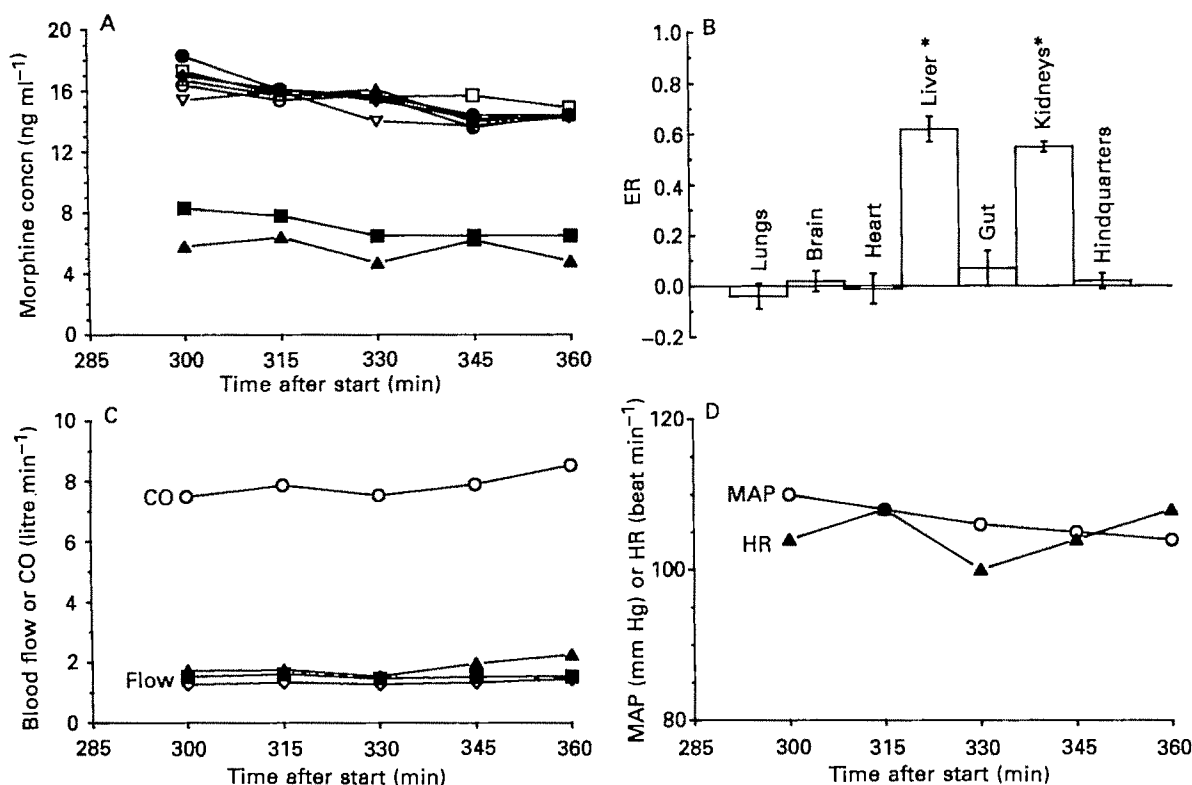


FIG. 1. A: Blood concentrations of morphine during the last 60 min of a 345-min maintenance infusion in sheep No. 4. A loading infusion of 20 mg h⁻¹ was administered for 15 min followed immediately by 2.5 mg h⁻¹ for 345 min. ● = Aorta; ○ = pulmonary artery; △ = sagittal sinus; □ = coronary sinus; ▲ = hepatic vein; ▽ = portal vein; ■ = renal vein; ◇ = posterior vena cava. B: Regional extraction ratios (ER) of morphine calculated from the morphine blood concentration data. In this study, significant (**P* < 0.05) extraction was found only across the liver and kidneys. C: Cardiac output (CO) and regional blood flows during the period of blood sampling described above. ○ = Cardiac output; ▲ = hepatic blood flow; ■ = renal blood flow; ◇ = hindquarter blood flow. D: Cardiovascular variables during the period described above. ○ = Mean arterial pressure (MAP); ▲ = mean heart rate (HR).

components [17]. There was no evidence of dose-dependent effects so the data for the different infusion rates in each of the animals were combined. The mean regional extraction ratios and clearances were examined by the one sample *t* test to determine if they were significantly different from zero. Other two-way comparisons were made using *t* tests for paired data. For all tests, *P* < 0.05 was considered statistically significant.

RESULTS

Data from a representative study (at the 2.5-mg h⁻¹ dose rate) are shown in figure 1. Cardiac output, regional blood flows, mean heart rate or mean arterial pressure did not alter systematically during morphine administration at any dose rate.

The total body and regional clearances of morphine were independent of dose rate across the 8-fold range of morphine maintenance infusion rates: the mean data for each animal were therefore combined. The overall mean (SEM) morphine *Cl* was 1.63 (0.21) litre min⁻¹. With the exception of the liver and kidneys, the mean arterial-regional venous concentration gradients were small: the mean regional extraction ratios and clearances of morphine are presented in table I. There was no systematic evidence of dose dependent extraction of morphine in any region (fig. 2). The corresponding overall regional clearances were liver 1.01 (0.10) litre min⁻¹ and kidneys 0.55 (0.06) litre min⁻¹. There was no relationship between any clearance and total body weight.

TABLE I. Mean (SEM) regional extraction ratios and clearances of morphine during i.v. infusion at steady state. In the absence of regional dose independence, the data for each of the four animals at four different infusion rates were combined. ** $P < 0.01$ compared with a value of 0

Region	Extraction ratio	Regional clearance (litre min ⁻¹)
Lung	0.05 (0.02)	0.29 (0.18)
Brain	-0.05 (0.04)	-0.01 (0.01)
Heart	-0.13 (0.04)	-0.03 (0.01)
Liver	0.68 (0.02)**	1.01 (0.10)**
Gut	-0.03 (0.04)	-0.04 (0.07)
Kidney	0.52 (0.05)**	0.55 (0.06)**
Hindquarter	-0.13 (0.08)	-0.12 (0.09)

Analysis of 48-h urine collection from eight animals accounted for 12.3 (2.7)% of the administered dose as unmetabolized morphine

(table II). With dose independent clearance, the expected value determined from the renal percentage of Cl was 37.1 (6.1)% ($P < 0.01$). The renal percentage of Cl was 34.8 (5.3)% in all 13 experiments. Using the combined information another way, the renal clearance measured indirectly from unmetabolized morphine urine concentrations was 0.21 (0.06) litre min⁻¹. This value is significantly different from the value of 0.55 (0.06) litre min⁻¹ measured directly ($P < 0.01$).

Tissue concentrations of morphine and the calculated tissue:blood partition coefficients determined at steady state for the four terminal morphine infusions are given in table III. From these experiments, despite inter-animal variability, there was no evidence of dose dependent tissue:blood partitioning of morphine. The median partition coefficients were lung 6.3, brain 2.1,

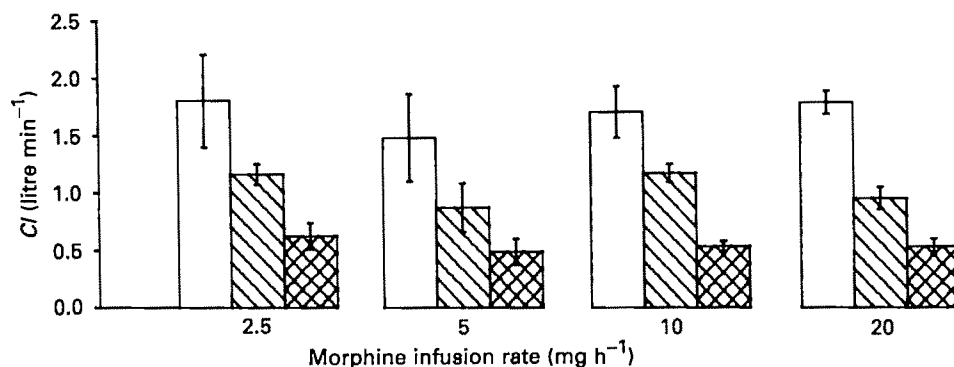


FIG. 2. Mean total body clearance □, liver clearance ▨ and kidney clearance ▩ of morphine at steady state during the different rates of infusion of morphine.

TABLE II. Renal clearance data for the eight experiments in which total urine recoveries to 48 h were made. ER_R = renal extraction ratio; Cl_R = renal clearance; Cl = mean total body clearance. ** Significantly different ($P < 0.01$); Student's t test for paired data. † Direct = measured directly from product of ER_R and renal blood flow; Indirect = measured indirectly from product of Cl and urinary recovery of unmetabolized morphine. ‡ Determined from the renal percentage of Cl

	Sheep number								Mean (SEM)
	1	1	2	2	3	4	4	4	
Dose (mg h ⁻¹)	2.5	5	2.5	20	5	2.5	10	20	
Mean ER_R	0.58	0.67	0.18	0.65	0.57	0.55	0.71	0.59	0.57 (0.06)
Cl (litre min ⁻¹)	2.33	1.17	1.13	1.64	0.95	2.08	2.14	1.70	1.64 (0.18)
Mean Cl_R (litre min ⁻¹)†									
Direct	0.58	0.65	0.16	0.57	0.63	0.84	0.52	0.62	0.57 (0.07)**
Indirect	0.69	0.11	0.14	0.11	0.14	0.16	0.12	0.14	0.21 (0.07)**
Urinary recovery of unmetabolized morphine									
Measured % dose (in urine to 48 h)	29.7	9.1	12.3	6.4	13.9	7.9	5.5	13.9	12.3 (2.7)**
Expected % dose‡	25.0	55.9	13.8	34.9	66.6	40.6	24.2	36.2	37.1 (6.1)**

TABLE III. Concentrations of morphine (as morphine base) in arterial blood (ng ml^{-1}) and tissue (ng g^{-1}) (Concn) at steady state, and calculated tissue:blood partition coefficients (Coeff.) after different maintenance infusions of morphine sulphate (Morphine)

Sample	Morphine 2.5 mg h^{-1} (Sheep No. 3)		Morphine 5 mg h^{-1} (Sheep No. 4)		Morphine 10 mg h^{-1} (Sheep No. 2)		Morphine 20 mg h^{-1} (Sheep No. 1)	
	Concn	Coeff.	Concn	Coeff.	Concn	Coeff.	Concn	Coeff.
Arterial blood	31		19		93		169	
Lung	191	6.2	169	8.9	260	2.8	1066	6.3
Brain	48	1.6	62	3.2	113	1.2	447	2.6
Heart	65	2.0	69	2.6	138	1.5	554	2.6
Liver	189	11.5	186	15.4	38	1.0	844	8.2
Gut (small bowel)	320	10.4	219	11.5	188	2.0	9471	55.9
Kidney	73	4.0	83	6.1	126	2.3	387	3.5
Hindquarter muscle	92	3.0	64	3.4	145	1.6	562	3.3
Hindquarter fat	5	0.2	5	0.3	14	0.2	17	0.1

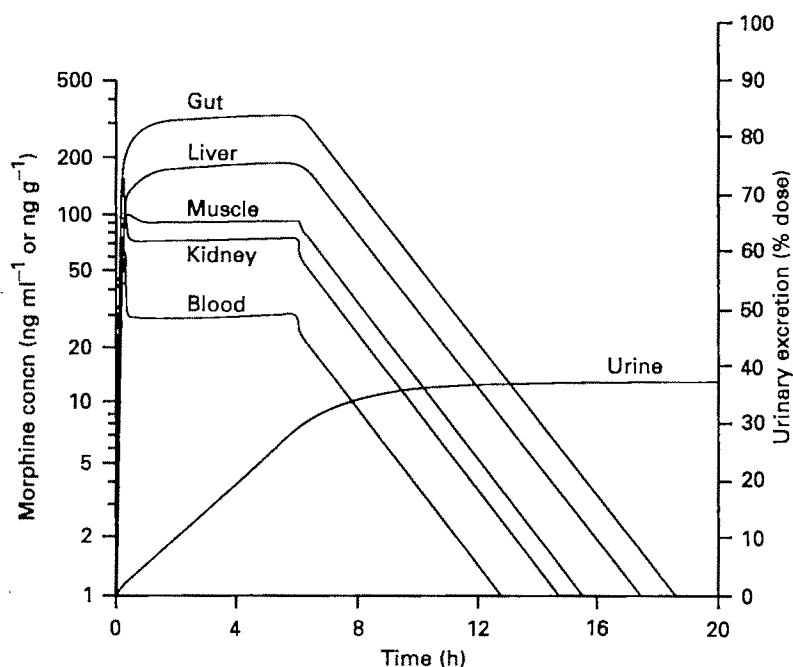


FIG. 3. Simulated time courses of blood (ng ml^{-1}) and tissue (ng g^{-1}) concentrations of morphine for the 2.5- mg h^{-1} infusion regimen. There is close agreement with the values found at 6 h and reported in table III.

heart muscle 2.3, liver 9.9, small bowel 11.0, kidney 3.8, hindquarter muscle 3.2 and hindquarter fat 0.2. Simulated values of time course of blood, liver, kidney, muscle concentrations and of urinary excretion of morphine for the 2.5- mg h^{-1} regimen (fig. 3) agree closely with the measured values reported in table III and elsewhere. From the simulated blood concentrations of morphine a slow half-life of 86 min was determined and this,

too, is in close agreement with the value derived from the preliminary study involving a 10-min infusion of morphine and compartment analysis.

DISCUSSION

This study would appear to be the first in which a regional pharmacokinetic-mass balance approach [18] has been applied to morphine.

Most previous studies have been based upon pharmacokinetic compartmental analysis of systemic blood samples to determine the *Cl* of morphine. Thus the impact of specific organ dysfunction on morphine kinetics would not have been revealed by such study designs, as the balance between the sites and rates of clearance may be altered without a net change in the global pharmacokinetic parameters of *Cl*, half-life and apparent volume of distribution.

One important finding of this study was that, within the dose range used, there was no evidence for significant cardiovascular effects or for dose- or time-dependent kinetics of morphine at any region. This may not pertain for much greater doses, at which morphine itself may cause significant cardiovascular disturbances and thereby affect its own disposition [19]. The most important finding, however, was that morphine disposition is more complex than generally perceived. While this study confirmed that the liver is the principal organ for the clearance of morphine, accounting for a mean of 62% of *Cl*, the kidneys accounted for 35%. In the absence of significant dose-related kidney clearance of morphine (as has been confirmed in the dog [19]), approximately 35% of the administered morphine dose should have been recovered from the urine if the kidney clearance was solely a result of excretion of unmetabolized morphine into urine. As only 13% of the morphine dose was recovered (table II), we conclude that the kidneys are metabolizing, as well as excreting, morphine. Indeed, this would be consistent with data showing the formation of morphine glucuronide in microsomes prepared from human kidney specimens [10].

The role of the kidney in morphine clearance has been debated vigorously in recent years, with the specificity of the morphine assay being of critical importance. Early work by Moore and others [3] using a radioimmunoassay (RIA) technique reported that decreased clearance of morphine occurred during renal transplantation in man; however, when this study was repeated using a specific RIA technique, no alteration of morphine kinetics was found [4]. In the period between these two reports others, using improved analytical techniques, studied the pharmacokinetics of morphine in subjects with normal kidneys and patients with renal dysfunction. For example, studies by Aitkenhead and colleagues [20] and by Säwe and Odar-Cederlöf [21] using a specific

HPLC method of morphine analysis of peripheral blood samples after a single i.v. morphine bolus found no difference in clearance of morphine between uraemic patients and control subjects, suggesting a minimal role of the kidney in the clearance of morphine. However, it is important to re-emphasize that central or peripheral venous plasma samples cannot be used to infer regional drug kinetics, as these cannot be determined except by regional sampling. The absence of a significant difference in morphine *Cl* between uraemic patients and patients with normal kidney function may represent compensatory extrahepatic, extrarenal clearance, as has been suggested for morphine disposition in patients with diabetes mellitus [22].

Studies in humans, dogs and goats have reported systemic plasma morphine clearance in excess of liver plasma flow [5-8, 19, 23]. For example, Mazoit and colleagues [5] found in normal volunteers a total plasma clearance of morphine $33.5 \text{ ml min}^{-1} \text{ kg}^{-1}$ —a value well in excess of putative hepatic plasma flow. Patwardhan and co-workers [9] found normal elimination of morphine in cirrhotic patients. Others have reported that the clearance of morphine is reduced, but still present, in hepatectomized dogs [24]. These results, taken together, are consistent with significant extrahepatic morphine clearance. Although there may be species differences, it is noted that the urinary excretion of unmetabolized morphine in humans [1] and dogs [19] is similar to that reported here in sheep. Morphine metabolism in gut wall of rats has been shown to occur [25]. Direct studies need to be performed to assess if human gut does metabolize morphine. In the absence of a significant mean arterio-portal gradient, we were unable to demonstrate any net clearance of morphine in the gut of sheep, although in some individual experiments net positive or negative mean extraction ratios were noted. This variability could have been related to the timing of the sampling period with respect to gastric emptying, recycling of morphine that was ion-trapped in gastric contents, or both. Although there was not a significant net clearance of morphine in the lungs, there was a net positive mean extraction ratio in nine of the 13 experiments (and in both of two pilot experiments [data not reported]). This should not be confused with first pass extraction which is known to occur for morphine and a variety of other drugs [26]. The

lungs are known to be a source of drug metabolizing enzymes and their role in the clearance of morphine still requires more detailed mass balance studies than have been performed to date. The ability of the human brain *in vitro* to metabolize morphine to M3G and M6G [27] has been demonstrated recently; however, the present study showed no significant net morphine clearance by the sheep brain. This may reflect a low rate of metabolism in brain compared with other tissues *in vivo*, resulting in an inability to demonstrate extraction across the brain.

The calculated tissue:blood morphine partition coefficients were greater than unity in all tissues except (hindquarter) fat. The partition coefficient of 0.2 in fat is consistent with the poor lipophilicity of morphine [28]. The partitioning of morphine into tissues provides morphine stores that could be mobilized with changes in regional blood flow or acid-base balance, although the magnitude of these effects is unknown. The mean brain:blood partition coefficient of 2.1 is greater than has been found in humans [29], rats [30] and dogs [31], which may be a reflection of any, or all, differences in species, morphine assay and experimental design. In other studies on the physiological disposition of morphine in the pregnant rat, tissue:plasma partition coefficients were reported to be concentration-independent, except for skeletal muscle, in which non-linear partitioning was suggested [16]. Although derived from only a small number of animals, the present study found no evidence for concentration-dependent tissue:blood partition coefficients in any tissues, including hindquarter muscle. The partition coefficients in sheep No. 2 were consistently the smallest values among sheep in all tissues, confirming the suggestion that interindividual variation in tissue:blood distribution and binding contributes a major source of interindividual pharmacokinetic differences [16].

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REFERENCES

1. Brunk SF, Delle M. Morphine metabolism in man. *Clinical Pharmacology and Therapeutics* 1974; 16: 51-57.
2. Säwe J. High dose morphine and methadone in cancer patients. Clinical pharmacokinetic considerations of oral treatment. *Clinical Pharmacokinetics* 1986; 11: 87-106.
3. Moore RA, Sear JW, Baldwin D, Allen M, Hunnisset A, Bullingham R, McQuay H. Morphine kinetics during and after renal transplantation. *Clinical Pharmacology and Therapeutics* 1984; 35: 641-645.
4. Sear JW, Hand CW, Moore RA, McQuay HJ. Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites. *British Journal of Anaesthesia* 1989; 62: 28-32.
5. Mazoit JX, Sandouk P, Zetlaoui P, Scherrmann JM. Pharmacokinetics of unchanged morphine in normal and cirrhotic subjects. *Anesthesia and Analgesia* 1987; 66: 293-298.
6. Dahlström B, Tamsen A, Paalzow L, Hartvig P. Patient-controlled analgesic therapy. IV: Pharmacokinetics and analgesic plasma concentrations of morphine. *Clinical Pharmacokinetics* 1982; 7: 266-279.
7. Sitar DS, Duke PC, Owen JA, Berger L, Mitenko PA. Kinetic disposition of morphine in young males after intravenous loading and maintenance infusion. *Canadian Anaesthetists Society Journal* 1986; 33: 145-149.
8. Olkkola KT, Maunukela E-L, Korpela R, Rosenberg PH. Kinetics and dynamics of postoperative intravenous morphine in children. *Clinical Pharmacology and Therapeutics* 1988; 44: 128-136.
9. Patwardhan RV, Johnson RF, Hoyumpa A Jr, Sheehan JJ, Desmond PV, Wilkinson GR, Branch RA, Schenker S. Normal metabolism of morphine in cirrhosis. *Gastroenterology* 1981; 81: 1006-1011.
10. Yue Q, Odar-Cederlöf I, Svensson JO, Säwe J. Glucuronidation of morphine in human kidney microsomes. *Pharmacology et Toxicology* 1988; 63: 337-341.
11. Runciman WB, Ilsley AH, Mather LE, Carapetis RJ, Rao MM. A sheep preparation for studying interactions between blood flow and drug disposition. I: Physiological profile. *British Journal of Anaesthesia* 1984; 56: 1015-1028.
12. Mather LE, Selby DG, Runciman WB. Effects of propofol and of thiopentone anaesthesia on the regional kinetics of pethidine in the sheep. *British Journal of Anaesthesia* 1990; 65: 365-372.
13. McLean CF, Mather LE, Odontiadis J, Sloan PA. Improved method for morphine determination in biological fluids and tissues: rapid, sensitive, selective. *Journal of Pharmacy and Pharmacology* 1990; 42: 669-671.
14. Hales JRS. Radioactive microsphere measurement of cardiac output and regional tissue blood flow in the sheep. *Pflügers Archiv* 1973; 344: 119-132.
15. Robinson BS, Snoswell AM, Runciman WB, Kuchel TR. Choline biosynthesis in sheep. *Biochemical Journal* 1987; 244: 367-373.
16. Gabrielsson JL, Paalzow LK. A physiological pharmacokinetic model for morphine disposition in the pregnant rat. *Journal of Pharmacokinetics and Biopharmaceutics* 1983; 11: 147-163.
17. Keppel GL. *Design and Analysis: A Researcher's Handbook*. Englewood Cliffs: Prentice-Hall Inc., 1973; 414-420.
18. Upton RN, Mather LE, Runciman WB, Nancarrow C, Carapetis RJ. The use of mass balance principles to describe regional drug distribution and elimination.

- Journal of Pharmacokinetics and Biopharmaceutics* 1988; 16: 13-29.
19. Garrett ER, Jackson AJ. Pharmacokinetics of morphine and its surrogates III: Morphine and morphine 3-glucuronide pharmacokinetics in the dog as a function of dose. *Journal of Pharmaceutical Sciences* 1979; 68: 753-771.
 20. Aitkenhead AR, Vater M, Achola K, Cooper CMS, Smith G. Pharmacokinetics of single-dose i.v. morphine in normal volunteers and patients with end-stage renal failure. *British Journal of Anaesthesia* 1984; 56: 813-818.
 21. Säwe J, Odar-Cederlöf I. Kinetics of morphine in patients with renal failure. *European Journal of Clinical Pharmacology* 1987; 32: 377-382.
 22. Persson MP, Wiklund L, Hartvig P, Paalzow L. Potential pulmonary uptake and clearance of morphine in postoperative patients. *European Journal of Clinical Pharmacology* 1986; 30: 567-574.
 23. Andersen HB, Christensen B, Findlay JWA, Jansen JA. Pharmacokinetics of intravenous, intrathecal and epidural morphine and fentanyl in the goat. *Acta Anaesthesiologica Scandinavica* 1986; 30: 393-399.
 24. Jacqz E, Ward S, Johnson R, Schenker S, Gerkens J, Branch RA. Extrahepatic glucuronidation of morphine in the dog. *Drug Metabolism and Disposition* 1986; 14: 627-630.
 25. Dahlström BE, Paalzow LK. Pharmacokinetic interpretation of the enterohepatic recirculation and first-pass elimination of morphine in the rat. *Journal of Pharmacokinetics and Biopharmaceutics* 1978; 6: 505-519.
 26. Roerig DL, Kotrly KJ, Vucins EJ, Ahlf SB, Dawson CA, Kampine JP. First pass uptake of fentanyl, meperidine and morphine in the human lung. *Anesthesiology* 1987; 67: 466-472.
 27. Wahlström A, Winblad B, Bixo M, Rane A. Human brain metabolism of morphine and naloxone. *Pain* 1988; 35: 121-127.
 28. Kaufman J, Semo NM, Koski WS. Microcoulometric titration of the pK_a 's and partition coefficients of narcotics and narcotic antagonists and their pH and their temperature dependence. *Journal of Medicinal Chemistry* 1975; 18: 647-655.
 29. Cravey RH, Reed D. The distribution of morphine in man following chronic intravenous administration. *Journal of Analytical Toxicology* 1977; 1: 166-167.
 30. Bolander H, Kourtopoulos H, Lundberg S, Persson S-Å. Morphine concentrations in serum, brain and cerebrospinal fluid in the rat after intravenous administration of a single dose. *Journal of Pharmacy and Pharmacology* 1983; 35: 656-659.
 31. Finck AD, Berkowitz BA, Hempstead J, Ngai SH. Pharmacokinetics of morphine: effects of hypercarbia on serum and brain morphine concentrations in the dog. *Anesthesiology* 1977; 47: 407-410.

COMPARISON BETWEEN SEVOFLURANE AND HALOTHANE FOR PAEDIATRIC AMBULATORY ANAESTHESIA

Y. NAITO, S. TAMAI, K. SHINGU, R. FUJIMORI AND K. MORI

SUMMARY

We have compared the rapidity and quality of recovery after sevoflurane anaesthesia with those after halothane anaesthesia. Thirty unpremedicated paediatric outpatients undergoing pulsed-dye laser therapy for port-wine stains were allocated randomly to receive either halothane or sevoflurane anaesthesia. Each group received 60% nitrous oxide and 1.0–1.5 MAC of volatile agent in oxygen for approximately 40 min. Patients receiving sevoflurane exhibited more rapid emergence and a significantly shorter postoperative recovery time compared with those receiving halothane. No major adverse effects were encountered in each group. These results suggest that sevoflurane anaesthesia is preferable to halothane anaesthesia for paediatric ambulatory patients.

KEY WORDS

Anaesthesia: paediatric. Anaesthetics, volatile: halothane, sevoflurane. Recovery: ambulatory surgery.

Sevoflurane has a low blood/gas partition coefficient and has been suggested to be useful for outpatients because of its rapid uptake and elimination [1]. It is not clear, however, if recovery from anaesthesia occurs more rapidly and completely in the ambulatory patient after this agent. To assess the usefulness of sevoflurane for outpatient anaesthesia in children, we have compared the rapidity and quality of recovery from general anaesthesia in paediatric patients who received either sevoflurane or halothane anaesthesia.

PATIENTS AND METHODS

We studied 30 paediatric ambulatory patients (ages 1–7 yr) undergoing pulsed-dye laser therapy for port-wine stain of their face and neck region under general anaesthesia without premedication [2]. Patients were allocated randomly to two groups to receive either halothane or sevoflurane. The study was approved by the Ethics Committee of our university and informed verbal consent was obtained from parents before operation. The patients had been fasting at least 6 h and received no premedication.

Anaesthesia was administered by the same anaesthetist. Induction of anaesthesia was by inhalation of 60% nitrous oxide and 0.5–2.5 MAC of halothane (1.0 MAC = 0.8%) or sevoflurane (1.0 MAC = 1.7%) in oxygen via either a Jackson-Rees system (body weight < 10 kg) or a paediatric semi-closed circle system (body weight ≥ 10 kg). Both agents were introduced gradually to the breathing system; concentrations were increased by increments of 0.5–1.0% every 2–3 breaths. After induction of anaesthesia, an i.v. cannula was inserted and atropine 0.01 mg/kg body weight was administered to prevent excessive salivation. Anaesthesia was maintained with 60% nitrous oxide and 1.0–1.5 MAC of the appropriate volatile agent in oxygen without tracheal intubation. Administration of nitrous oxide and volatile anaesthetic agent was discontinued at the end of operation. After awak-

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TABLE I. Details of the 30 patients studied and their anaesthesia. *B.wt.* = Body weight; *Induction* = time between induction and loss of eyelash reflex; *Duration* = duration of induction and maintenance of anaesthesia; *Emergence* = time from discontinuation of inhalation agent to opening eyes on request; *Recovery* = time from discontinuation of inhalation agent to discharge

Patient No.	Age (yr)	Sex	B.wt (kg)	Induction (min)	Duration (min)	Emergence (min)	Recovery (min)	Vomiting	Restlessness agitation
Halothane group									
1	6	M	16	3	22	11	157		
2	1	M	10	3	31	4	151		+
3	3	F	14	2	54	7	111		
4	1	M	13	3	46	9	120		
5	6	F	20	3	76	16	132		
6	1	F	9	3	44	10	125	+	+
7	1	M	10	4	55	8	165		
8	1	F	10	5	45	10	110		
9	1	M	10	3	25	10	120		
10	5	F	17	5	32	6	141		
11	6	F	18	4	23	12	160		
12	7	M	22	3	53	10	115	+	+
13	3	F	17	3	45	10	170		
14	3	F	16	3	35	11	160		
15	6	F	20	3	31	9	124		
Mean (SD)	3.4 (2.3)		14.8 (4.2)	3.3 (0.8)	41.1 (14.2)	9.5 (2.7)	137.4 (20.6)		
Sevoflurane group									
16	5	M	17	2	43	5	115		+
17	7	M	22	5	40	6	104		+
18	6	M	15	5	25	5	60		
19	6	F	20	3	44	5	55		+
20	3	F	16	3	38	4	65		
21	2	F	10	4	46	4	60		
22	2	M	13	2	25	5	85		+
23	1	F	6	3	38	3	70		
24	1	M	13	2	30	3	65		+
25	3	F	15	2	46	5	100		
26	2	F	11	1	37	3	95		+
27	1	F	7	5	20	5	110		
28	1	M	10	2	46	2	120		+
29	5	F	20	5	55	5	120	+	+
30	2	F	14	5	30	5	90		+
Mean (SD)	3.1 (2.0)		13.9 (4.5)	3.2 (1.4)	41.5 (8.5)	4.3 (1.1)	87.6 (22.7)		
P	ns	—	ns	ns	ns	< 0.01	< 0.01	ns	ns

ening, patients were transferred to the post-operative recovery room and cared for by a specially trained nursing staff with the parents present. Postoperative restlessness, agitation and vomiting were recorded. Postoperative pain was treated by rectal administration of indomethacin suppository 1 mg kg⁻¹ if necessary. Recovery of cognitive and psychomotor function was assessed by the nurse, who was not informed which anaesthetic had been used. The decision to discharge was made by the anaesthetist, on the basis of the following criteria [1, 3]: age-appropriate level of alertness; age-appropriate level of ambulation; stable vital sign for ≥ 30 min; absence of nausea or vomiting for ≥ 30 min;

tolerance of oral fluid; pain controllable with indomethacin suppository; absence of bleeding.

Halothane and sevoflurane were administered via appropriate calibrated vaporizers (halothane: Acoma, Vaporizer F; sevoflurane: Ohmeda, Sevotec 3).

Time between induction and loss of eyelash reflex (induction), duration of induction and maintenance of anaesthesia (duration), time from discontinuation of the inhalation agent to opening the eyes on request (emergence), and time from discontinuation of the inhalation agent to discharge (recovery) were recorded.

Data are presented as mean (SD). Statistical analysis was performed using the Student's *t* test

(unpaired) for parametric data, or the chi-square test.

RESULTS

There was no significant difference in characteristics between the two groups (table I). Induction time and duration of anaesthesia were similar in both groups, but significantly more rapid emergence was observed in the sevoflurane group: halothane 9.5 (2.7) min; sevoflurane 4.3 (1.1) min. Recovery time in the sevoflurane group was significantly shorter than that in the halothane group: halothane 137.4 (20.6) min; sevoflurane 87.6 (22.7) min.

No significant complications such as laryngospasm, cyanosis, rigidity or movement were observed in the two groups. Vomiting was observed in two patients in the halothane group and one in the sevoflurane group; all episodes were observed after emergence. The number of patients who exhibited postoperative restlessness and agitation was greater in the sevoflurane group (9/15) than in the halothane group (3/15) (not significant). Postoperative restlessness and agitation in these patients were treated effectively with indomethacin in all patients, without any apparent changes in consciousness and vital signs.

DISCUSSION

Anaesthetics used for paediatric outpatient surgery should produce rapid and smooth induction, rapid emergence and a short postoperative recovery period with minimal adverse effects [3]. Thus anaesthesia for such patients is generally induced and maintained with inhalation of volatile anaesthetics, especially halothane, in combination with nitrous oxide [1, 3–5]. The rapidity of recovery from inhalation anaesthesia depends on the solubility of the volatile anaesthetics [1, 6, 7]. The blood/gas partition coefficient of sevoflurane is 0.69 [8], which is comparable to that of nitrous oxide (0.46), therefore, sevoflurane should be expected to produce a more rapid and complete emergence [1]. Our present study clearly demonstrated that the times required for emergence and recovery in patients anaesthetized with sevoflurane and nitrous oxide were significantly shorter than those in patients receiving halothane and nitrous oxide. These results indicate that the use of sevoflurane in the paediatric outpatient setting reduces hospital stay.

The incidence of postoperative restlessness and agitation seemed to be greater in the patients anaesthetized with sevoflurane. As all of these patients were treated effectively with indomethacin, it is suggested that these symptoms are caused by pain during emergence and the immediate postoperative period [9]. No apparent delay in discharge was observed in these patients. These phenomena might reflect the rapidity and completeness of emergence from sevoflurane anaesthesia.

It should be noted that there was no serious complication associated with the inhalation of sevoflurane. The incidence of postoperative vomiting was low in the patients anaesthetized with sevoflurane. As vomiting is a major cause of delayed discharge from the recovery room and unscheduled overnight admissions [3], the low incidence of postoperative vomiting, which has been confirmed in a much larger clinical trial of sevoflurane in paediatric anaesthesia [10], should encourage the use of this anaesthetic agent in paediatric ambulatory surgery.

REFERENCES

1. White PF. Outpatient anesthesia. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone, 1990; 2025–2059.
2. Achauer EM, Vander Kam VM, Miller SR. Clinical experience with the pulsed-dye laser in the treatment of capillary malformations (port-wine stains): A preliminary report. *Annals of Plastic Surgery* 1990; 25: 344–352.
3. Oh TE, Davis PJ. Pediatric outpatient anesthesia. In: Motoyama EK, ed. *Smith's Anesthesia for Infant and Children*. St Louis: Mosby, 1990; 681–688.
4. Cattermole RW, Verghese C, Blair IJ, Jones CJH, Flynn PJ, Sebel PS. Isoflurane and halothane for outpatient dental anaesthesia in children. *British Journal of Anaesthesia* 1986; 58: 385–389.
5. Kingston HGG. Halothane and isoflurane anaesthesia in pediatric outpatients. *Anesthesia and Analgesia* 1986; 65: 181–184.
6. Davidson SH. A comparative study of halothane and enflurane in paediatric outpatient anaesthesia. *Acta Anaesthesiologica Scandinavica* 1978; 22: 58–63.
7. Valanne JV, Korttila K. Recovery following general anaesthesia with isoflurane or enflurane for outpatient dentistry and oral surgery. *Anesthetic Progress* 1988; 35: 48–52.
8. Strum DP, Eger EI II. Partition coefficients for sevoflurane in human blood, saline, and olive oil. *Anesthesia and Analgesia* 1987; 66: 654–656.
9. Motoyama EK. Recovery from anesthesia. In: Motoyama EK, ed. *Smith's Anesthesia for Infant and Children*. St Louis: Mosby, 1990; 313–330.
10. Morisaki H, Suzuki G, Miyazawa N, Kiuchi Y, Misaki T, Suzuki A. A clinical trial of sevoflurane in children for herniorrhaphy. *Journal of Anesthesia* 1988; 2: 94–97.

MIDAZOLAM MODIFIES PANCREATIC AND ANTERIOR PITUITARY HORMONE SECRETION DURING UPPER ABDOMINAL SURGERY

J. P. DESBOROUGH, G. M. HALL, G. R. HART AND J. M. BURRIN

SUMMARY

We have investigated the effects of midazolam on circulating concentrations of pituitary and pancreatic hormones in eight healthy patients during cholecystectomy and compared the changes with those in a control group of eight patients. Anaesthesia was induced either with midazolam 0.42 mg kg^{-1} i.v. followed by an infusion of midazolam 0.125 mg kg^{-1} for 1 h, or with a sleep dose of thiopentone. All patients received vecuronium, and the lungs were ventilated with 0.5–1.0% halothane and 70% nitrous oxide in oxygen. The use of midazolam was associated with a significant decrease ($P < 0.05$) in secretion of cortisol and insulin during surgery. Serum growth hormone secretion was augmented, but this did not reach statistical significance. There was little difference in the concentrations of circulating metabolites between the two groups, except for a significant decrease in blood glucose ($P < 0.05$) in the midazolam group after 60 min. There were no marked differences in cardiovascular variables between the two groups of patients.

KEY WORDS

Hypnotics, benzodiazepines: midazolam. Hormones: cortisol, growth hormone, insulin. Surgery: cholecystectomy.

Midazolam is an imidazobenzodiazepine used for induction and maintenance of anaesthesia, and for sedation. Its pharmacology and clinical effects have been reviewed by Reves and colleagues [1]. Central actions of benzodiazepines are mediated via multi-subunit GABA_A receptors which have binding sites for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Benzodiazepines facilitate the synaptic effects of GABA, which modifies chloride ion conductance. GABA_A

receptors have been demonstrated in the CNS and in the periphery [2, 3]. In addition, benzodiazepine receptors, not linked with GABA, are present in high concentrations in peripheral tissues and in the CNS [4].

The effects of GABA agonists, including benzodiazepines, on pituitary hormone secretion have been studied extensively [5]. In general, GABA agonists reduce the secretion of adrenocorticotrophic hormone (ACTH) and consequently cortisol, and stimulate basal secretion of growth hormone (GH). Studies of the effects of GABA agonists on hormone secretion from the endocrine pancreas have shown contrasting results [6, 7], but indicate that GABA may also have a role in pancreatic endocrine function.

Several groups have investigated the modification by midazolam of the hormonal and metabolic response to surgery and these studies have been reviewed recently [8]. The results of some studies may have been influenced by the concomitant use of potent opioids [9–11] which are known to affect hypothalamic-pituitary hormone secretion [12]. The object of the present study, therefore, was to investigate further the specific effects of midazolam on the hormonal and metabolic responses to upper abdominal surgery.

PATIENTS AND METHODS

We studied 16 healthy patients admitted for elective cholecystectomy. None had a history of diabetes mellitus or other endocrine disorder. All

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patients gave written informed consent to the study, which was approved by the Hospital Ethics Committee. Patients were allocated randomly to receive either midazolam 0.42 mg kg^{-1} i.v. over 5 min followed by an infusion of 0.125 mg kg^{-1} i.v. for 1 h, or an induction dose of thiopentone.

All studies were started before 10:00. Patients were premedicated with papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. 90 min before induction of anaesthesia. On arrival in the anaesthetic room, a central venous catheter was placed percutaneously via a vein in the antecubital fossa for sampling of blood and administration of drugs and i.v. fluids. Approximately 30 min before the start of surgery (–30 min), a control blood sample was collected and mean arterial pressure and heart rate were measured.

Anaesthesia was induced in the control group with a dose of i.v. thiopentone sufficient to abolish the eyelash reflex, and in the midazolam group with midazolam 0.42 mg kg^{-1} i.v. In the midazolam group, an infusion of midazolam 1 mg ml^{-1} at a rate of 0.125 mg kg^{-1} for 1 h only was started before surgery commenced. All patients received vecuronium 0.1 mg kg^{-1} to facilitate intubation of the trachea, and the lungs were ventilated with 0.5–1.0% halothane and 70% nitrous oxide in oxygen. Ventilation was adjusted to maintain an end-tidal partial pressure of carbon dioxide 4.0–4.5 kPa.

Sodium chloride 0.9% was infused at a rate of $6 \text{ ml kg}^{-1} \text{ h}^{-1}$ during surgery and $2 \text{ ml kg}^{-1} \text{ h}^{-1}$ after the end of surgery in all patients. After antagonism of neuromuscular block, increments of flumazenil 0.1 mg were given to patients in the midazolam group if necessary to restore adequate spontaneous ventilation. All patients received papaveretum 5 mg i.v. on demand for analgesia in the recovery period.

Blood samples were collected at the start of surgery (0 min) and 30, 60, 90, 120, 240 and 360 min after the start of surgery. Heart rate and mean arterial pressure were measured at the same time as blood sampling. Blood samples were analysed in duplicate for PCV, glucose, lactate, non-esterified fatty acids (NEFA), cortisol, growth hormone (GH) and insulin concentrations as described previously [13]. Investigators were unaware of the sample identities at the time of analysis.

The samples were analysed for hormones in two batches. The intra-assay coefficients of variation for cortisol were 7% and 4% at 144 and

478 nmol litre^{-1} , respectively, for GH 5% and 8% at 4.4 and 11.8 mu litre^{-1} , respectively, and for insulin 10% at 9.2 mu litre^{-1} . The interassay coefficients of variation for cortisol were 11% and 8% at 144 and 493 nmol litre^{-1} , respectively, for GH 13% and 12% at 4.6 and 11.9 mu litre^{-1} , respectively and for insulin 10% at 9.4 mu litre^{-1} .

Results are shown as mean (SEM) or median (range) for GH data which were not normally distributed. Data were analysed by one- or two-way analysis of variance with Dunnett's test as appropriate, and by Wilcoxon rank sum test and Wilcoxon signed rank test for GH data.

RESULTS

There was no difference between the groups in age, weight, duration of surgery or dose of papaveretum received (table I). The mean time interval from the start of induction of anaesthesia

TABLE I. Details of patients studied (mean (range or SEM))

	Control (n = 8)	Midazolam (n = 8)
Age (yr)	52.1 (24–72)	47.0 (24–70)
Weight (kg)	69.8 (2.8)	62.6 (3.7)
Sex (F:M)	5:3	8:0
Duration of surgery (min)	98 (15.3)	86 (7.6)
Total dose of midazolam (mg)		34.1 (1.1)
Post op. papaveretum (mg)	17.5 (1.1)	15.7 (1.1)

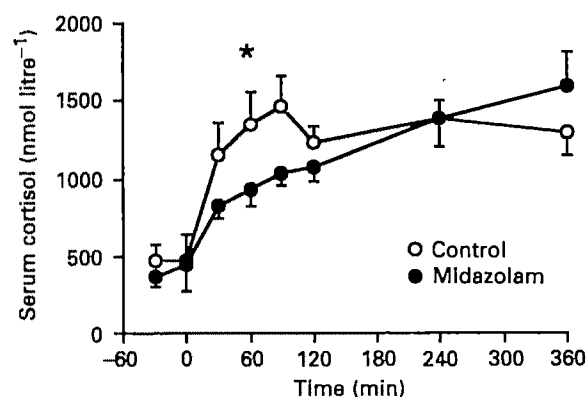


FIG. 1. Mean (SEM) serum concentrations of cortisol in control and midazolam groups. 0 min = Start of surgery. Significant difference between groups: * $P < 0.05$.

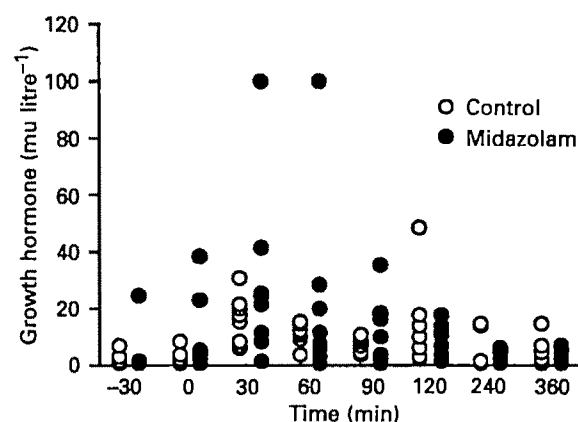


FIG. 2. Individual serum concentrations of growth hormone in control and midazolam groups. 0 min = Start of surgery.

to the start of surgery was 17.5 min in the control group and 20.6 min in the midazolam group. In patients receiving midazolam, surgery commenced 5.6 min after the infusion was started. The mean (SEM) induction dose of midazolam was 26.3 (1.6) mg and the total dose was 34.1 (1.1) mg. Three patients in the midazolam group received flumazenil on completion of surgery after antagonism of neuromuscular block: two received 0.2 mg and one received 0.5 mg. In all three patients, flumazenil was given after the 90-min blood sample had been collected. Blood loss did not exceed 300 ml in any patient and no patient received blood transfusion during the study.

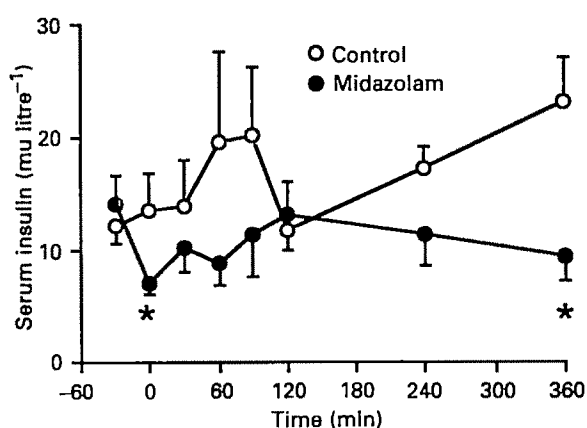


FIG. 3. Mean (SEM) serum concentrations of insulin in control and midazolam groups. 0 min = Start of surgery. Significant difference between groups: * $P < 0.05$.

Serum cortisol (fig. 1)

In the control group of patients, serum concentrations of cortisol increased significantly during surgery from 466 nmol litre⁻¹ to 1155 nmol litre⁻¹ ($P < 0.01$) after 30 min and reached 1465 nmol litre⁻¹ ($P < 0.01$) after 90 min. This significant increase in serum concentration of cortisol ($P < 0.01$) persisted to the end of the study. In the midazolam group, cortisol concentrations increased more slowly, from 364 nmol litre⁻¹ to 830 nmol litre⁻¹ after 30 min ($P < 0.05$) and to 1034 nmol litre⁻¹ ($P < 0.05$)

TABLE II. Concentrations of blood glucose and lactate and plasma NEFA, and PCV. Within group differences from preinduction value (-30 min): * $P < 0.05$; ** $P < 0.01$. Between group differences: † $P < 0.05$

	Time of sample (min)							
	-30	0	30	60	90	120	240	360
Blood glucose (mmol litre ⁻¹)								
Control	4.79 (0.21)	5.32 (0.38)	6.93 (0.39)*	7.30 (0.50)**	6.51 (0.41)*	6.97 (0.53)*	7.01 (0.63)*	6.96 (0.65)*
Midazolam	4.90 (0.18)	4.98 (0.22)	6.43 (0.57)	5.84 (0.45)†	6.64 (0.56)*	6.52 (0.56)*	6.56 (0.44)*	6.13 (0.41)
Blood lactate (mmol litre ⁻¹)								
Control	1.03 (0.13)	0.92 (0.12)	1.01 (0.11)	0.95 (0.15)	0.88 (0.08)	0.84 (0.07)	0.66 (0.08)	0.58 (0.04)*
Midazolam	0.86 (0.12)	0.84 (0.10)	0.92 (0.15)	0.95 (0.15)	0.79 (0.10)	0.78 (0.11)	0.65 (0.13)	0.62 (0.10)
Plasma NEFA (mmol litre ⁻¹)								
Control	1.15 (0.11)	1.10 (0.15)	1.31 (0.16)	1.37 (0.13)	1.23 (0.06)	1.31 (0.19)	1.47 (0.17)	1.31 (0.09)
Midazolam	1.14 (0.17)	0.90 (0.13)	1.13 (0.21)	1.11 (0.19)	0.96 (0.14)	1.01 (0.06)	1.05 (0.13)	1.04 (0.09)†
PCV (%)								
Control	39.1 (1.3)	38.1 (1.6)	37.6 (1.4)	37.4 (1.8)	38.5 (2.1)	38.2 (1.8)	39.3 (1.6)	39.0 (1.6)
Midazolam	39.7 (1.2)	38.7 (1.1)	38.2 (1.6)	37.2 (1.2)	36.8 (2.3)	37.2 (1.6)	37.1 (1.5)	36.4 (1.6)

after 90 min. Cortisol values were significantly less in the midazolam group at 60 min compared with the control group (F 5.61, $P < 0.05$).

Serum growth hormone (fig. 2)

In the control group, GH values did not change significantly from preinduction values of 1.0 ($< 1-6.9$) to 1.4 ($< 1-8.3$) at the start of surgery (0 min), but increased to 16.4 (6.1–30.8) $\mu\text{U litre}^{-1}$ after 30 min of surgery. This significant increase ($P < 0.01$) persisted until 120 min after the start of surgery. In contrast, in the midazolam group, GH concentration increased significantly from preinduction values of 1.1 ($< 1-24.3$) to 4.0 ($< 1-38.6$) $\mu\text{U litre}^{-1}$ ($P < 0.05$) at the start of surgery (0 min) and increased further, to 23.2 (1.2– > 100) $\mu\text{U litre}^{-1}$, after 30 min of surgery. This significant increase ($P < 0.01$) was maintained until 90 min after surgery started. In spite of the augmented response in the midazolam group, there was no significant difference between the two groups at any time point studied.

Serum insulin (fig. 3)

In the control group, serum concentrations of insulin did not change significantly during the course of the study, but in the midazolam group concentrations decreased significantly after induction of anaesthesia, from 14.1 $\mu\text{U litre}^{-1}$ to 7.1 $\mu\text{U litre}^{-1}$ at the start of surgery ($P < 0.05$) and remained less than preinduction concentrations during surgery. Serum concentrations of insulin were significantly smaller in the midazolam group compared with the control group at 0 min (F 8.94, $P < 0.05$) and at 360 min (F 5.62, $P < 0.05$).

Circulating metabolites and PCV (table II)

Blood concentrations of glucose increased in the control group from 4.79 mmol litre^{-1} before induction to 7.30 mmol litre^{-1} after 60 min of surgery ($P < 0.01$). In the midazolam group, glucose values increased more slowly, from a preinduction value of 4.90 mmol litre^{-1} to 6.64 mmol litre^{-1} at 90 min ($P < 0.05$). Blood concentration of glucose was significantly less in the midazolam group at 60 min ($P < 0.05$).

Blood concentrations of lactate changed little in both groups during surgery, but declined in the postoperative period. This decrease was significant only in the control group at 360 min ($P < 0.05$). There were no significant differences in lactate values between groups.

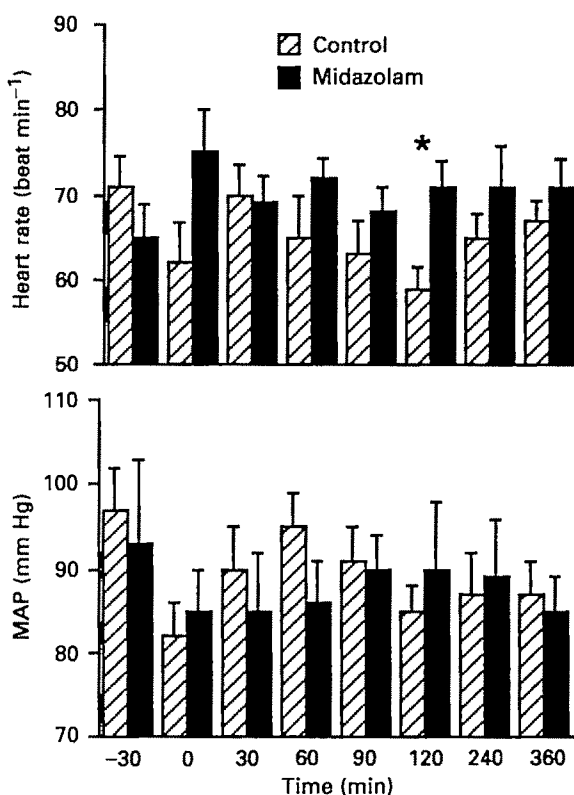


Fig. 4. Mean (SEM) heart rate and mean arterial pressure (MAP) in control and midazolam groups. 0 min = Start of surgery. Significant difference between groups: * $P < 0.05$.

There was no significant change in plasma NEFA concentrations in the two groups of patients. NEFA values were always smaller in the midazolam group than in the control group and this difference was significant at 360 min ($P < 0.05$).

There were no significant changes in PCV in each group during the study and no significant differences between the two groups.

Heart rate and mean arterial pressure (fig. 4)

Heart rate did not change significantly in the control group during the study. In the midazolam group, heart rate increased significantly from 65 to 75 beat min^{-1} at the start of surgery ($P < 0.05$) and remained greater than preinduction values during the study, although this change was not significant. Heart rate was significantly slower in the control group at 120 min compared with the midazolam group (F 9.15, $P < 0.05$).

Mean arterial pressure did not change signifi-

cantly in the two groups during the study, and there was no significant difference between groups.

DISCUSSION

Induction of anaesthesia with midazolam 0.42 mg kg^{-1} i.v. followed by an infusion of midazolam $0.125 \text{ mg kg}^{-1} \text{ h}^{-1}$ for 1 h in addition to halothane anaesthesia, produced a significant decrease in serum concentrations of cortisol and insulin, together with an increase in serum concentrations of growth hormone. The control group received thiopentone induction and halothane alone. Blood concentration of glucose was significantly smaller in the midazolam group at 60 min; otherwise, there were no significant differences in the concentrations of circulating metabolites between the two groups. There were no major differences in cardiovascular variables between the two groups.

Oral benzodiazepines have been shown to suppress cortisol concentrations in human studies [14]. Recent work suggests that GABA agonists may reduce the secretion of ACTH, and subsequently cortisol, through an inhibition of the secretion of hypothalamic corticotrophin releasing factor (CRF) [15, 16]. However, a direct effect on the adrenal glands cannot be excluded, as peripheral benzodiazepine receptors have been demonstrated in the rat adrenal cortex [17].

We have demonstrated a decrease in serum concentrations of cortisol at 60 min after the start of surgery in patients receiving midazolam. This is in contrast with a study by Dawson and Sear [9] in which no effect on the adrenocortical response to surgery was demonstrated when midazolam 20 mg was used as an induction agent compared with thiopentone $4\text{--}5 \text{ mg kg}^{-1}$, before fentanyl $3 \mu\text{g kg}^{-1}$, nitrous oxide and enflurane anaesthesia for hysterectomy. In their investigation, the induction dose of midazolam was smaller, no infusion was used and sampling was limited to preinduction, end of surgery and three post-operative samples. All these factors, particularly the absence of intraoperative samples, may be implicated in the failure of the study [9] to demonstrate any hormonal suppression with midazolam.

Our choice of dose of midazolam was based on a previous study by Nilsson and colleagues [10], in which midazolam was given in combination with large doses of alfentanil in a total i.v. technique. In their study the mean (SEM) dose of

midazolam was 39 (4) mg and that of alfentanil 17.5 (2.1) mg. Serum concentrations of cortisol decreased after induction of anaesthesia, remained small during pelvic surgery and increased to approximately $800 \text{ nmol litre}^{-1}$ only 4 h after the end of surgery. However, these results were not significantly different from the control group who received thiopentone and alfentanil (16.5 (2.4) mg). The use of alfentanil in this study may have masked any effect of midazolam on cortisol secretion, as opioids are known to inhibit the cortisol response to surgery [12].

Crozier and colleagues [11] showed that induction of anaesthesia with midazolam 0.2 mg kg^{-1} followed by an infusion of midazolam $0.09 \text{ mg kg}^{-1} \text{ h}^{-1}$ during minor body surface surgery decreased serum concentrations of cortisol and ACTH to an extent similar to etomidate 0.3 mg kg^{-1} followed by infusion of etomidate $0.36 \text{ mg kg}^{-1} \text{ h}^{-1}$. In contrast with etomidate, midazolam did not impair subsequent secretion of cortisol stimulated by exogenous ACTH. Midazolam attenuated β -endorphin secretion and ACTH secretion, which suggested a central site of action rather than an effect on adrenal steroidogenesis.

Flumazenil is a specific benzodiazepine antagonist. There are conflicting reports of its effects on hypothalamic-pituitary hormone secretion. *In vitro* studies have demonstrated that flumazenil may antagonize the inhibition of secretion of CRF induced by benzodiazepines [15]. Although we cannot exclude an effect of flumazenil on post-operative cortisol concentrations in our study, there were no marked differences in cortisol values in the three patients who received flumazenil compared with other patients in the midazolam group. Nilsson [8] reported no difference in postoperative concentrations of cortisol in patients receiving flumazenil after total i.v. anaesthesia with midazolam and alfentanil, compared with a similar group of patients who did not receive flumazenil. Furthermore, in a study in which flumazenil (mean dose 0.84 mg) was used to antagonize sedation after midazolam (mean dose 11.0 mg), no increases in β -endorphin or catecholamine concentrations were found compared with a control group [18].

The finding of a greater serum GH response, although not statistically significant, in patients receiving midazolam in the present study is consistent with many previous reports in which GABA agonists, including benzodiazepines, have

been shown to regulate secretion of GH in humans [19, 20]. In most studies, GABA agonists have a stimulatory effect on basal GH secretion, but inhibition of exercise-induced secretion of GH has been demonstrated, suggesting a dual role [20]. The precise mechanism is not fully understood, but GABA may modulate the actions of neurotransmitters involved in GH secretion.

The decrease in serum concentrations of insulin to 50% of resting values after induction of anaesthesia with midazolam 0.42 mg kg^{-1} was interesting. It is tempting to speculate that this might be caused by a direct effect of midazolam on insulin secretion from the pancreas. GABA has been demonstrated in animal and human pancreatic islets [21, 22] and more recently has been shown by immunocytochemistry to be localized with insulin in the β -cells of the rat pancreas [23]. A mechanism whereby GABA co-secreted with insulin may modulate glucagon secretion via GABA_A receptor stimulation has been reported [24]. Peripheral type benzodiazepine receptors exist also in rat pancreatic tissue [17], although numbers are much smaller than in the adrenal cortex. Human and animal studies have produced conflicting results of the effects of GABA agonists on insulin secretion [6, 7]: however, the findings suggest that GABA agonists may modulate endocrine pancreatic function. To our knowledge, a clinical effect of midazolam on secretion of insulin during surgery has not been reported previously, and this finding requires confirmation.

The marked changes in concentrations of cortisol, GH and insulin in the midazolam group had surprisingly little effect on the concentrations of circulating metabolites. Blood concentrations of glucose tended to be smaller throughout the study in the midazolam group, but this difference was significant only at 60 min. Control of glycaemia during surgery is influenced mainly by the extent of stimulation of the sympathetic adrenergic system. Crozier and colleagues showed that midazolam attenuated adrenaline concentrations during minor surgery [11]. It is possible that this was a direct effect, as GABA has been demonstrated in adrenal chromaffin cells and GABA receptors have been identified in the adrenal medulla [25].

The absence of significant changes in mean arterial pressure after the large dose of midazolam used in this study confirms previous reports showing minimal cardiovascular changes after induction of anaesthesia with midazolam.

Haemodynamic effects after midazolam $0.25\text{--}0.3 \text{ mg kg}^{-1}$ are similar to those seen with thiopentone $3\text{--}4 \text{ mg kg}^{-1}$ [26, 27].

In conclusion, we have shown that midazolam, when given in a large dose, modifies the endocrine response to surgery. Unlike potent opioids which have only an inhibitory effect on many pituitary hormones [12], midazolam has a mixed inhibitory and stimulatory effect on pituitary secretion, together with an inhibitory effect on pancreatic function.

REFERENCES

1. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: Pharmacology and uses. *Anesthesiology* 1985; 62: 310–324.
2. Erdo SL. Peripheral GABAergic mechanisms. *Trends in Pharmacological Sciences* 1985; 6: 205–208.
3. Ong J, Kerr DIB. GABA-receptors in peripheral tissues. *Life Sciences* 1990; 46: 1489–1501.
4. Verma A, Snyder SH. Peripheral type benzodiazepine receptors. *Annual Review of Pharmacology and Toxicology* 1989; 29: 307–322.
5. De Feudis FV. GABA and hormonal secretion. *Trends in Pharmacological Sciences* 1984; 5: 152–156.
6. Passariello N, Giugliano D, Torella R, Sgambato S, Coppola L, Frasca N. A possible role for γ -aminobutyric acid in the control of the endocrine pancreas. *Journal of Clinical Endocrinology and Metabolism* 1982; 54: 1145–1149.
7. Kawai K, Unger RH. Effects of γ -aminobutyric acid on insulin, glucagon and somatostatin release from isolated perfused dog pancreas. *Endocrinology* 1983; 113: 111–113.
8. Nilsson A. Autonomic and hormonal responses after the use of midazolam and flumazenil. *Acta Anaesthesiologica Scandinavica* 1990; 34 (Suppl. 92): 51–54.
9. Dawson D, Sear JW. Influence of induction of anaesthesia with midazolam on the neuro-endocrine response to surgery. *Anaesthesia* 1986; 41: 268–271.
10. Nilsson A, Persson MP, Hartvig P, Wide L. Effect of total intravenous anaesthesia with midazolam/alfentanil on the adrenocortical and hyperglycaemic response to abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1988; 32: 379–382.
11. Crozier TA, Beck D, Schlaeger M, Wuttke W, Kettler D. Endocrinological changes following etomidate, midazolam or methohexital for minor surgery. *Anesthesiology* 1987; 66: 628–635.
12. Desborough JP, Hall GM. Modification of the hormonal and metabolic response to surgery by narcotics and general anaesthesia. In: Bevan DR, ed. *Baillieres Clinical Anaesthesiology. Metabolic Response to Surgery*, Vol. 3. London: Baillière, 1989; 317–334.
13. Desborough JP, Edlin SA, Burrin JM, Bloom SR, Morgan M, Hall GM. Hormonal and metabolic responses to cholecystectomy: comparison of extradural somatostatin and diamorphine. *British Journal of Anaesthesia* 1989; 63: 508–515.
14. Gram LF, Cristensen L, Kristensen CB, Kragh-Sorensen P. Suppression of plasma cortisol after oral administration

- of oxazepam in man. *British Journal of Clinical Pharmacology* 1984; 17: 176-178.
15. Calogero AE, Gallucci WT, Chrousos GP, Gold PW. Interaction between GABAergic neurotransmission and rat hypothalamic corticotrophin-releasing hormone secretion *in vitro*. *Brain Research* 1988; 463: 28-36.
 16. Kalogeros KT, Calogero AE, Kuribayashi T, Khan I, Gallucci WT, Kling MA, Gold PW. *In vitro* and *in vivo* effects of the triazolobenzodiazepine Alprazolam on hypothalamic-pituitary-adrenal function: pharmacological and clinical implications. *Journal of Clinical Endocrinology and Metabolism* 1990; 70: 1462-1471.
 17. De Souza EB, Anholt RRH, Murphy KMM, Snyder SH, Kuhar MJ. Peripheral-type benzodiazepine receptors in endocrine organs: Autoradiographic localisation in rat pituitary, adrenal and testis. *Endocrinology* 1985; 116: 567-573.
 18. White PF, Shafer A, Boyle WA, van Doze A, Duncan S. Benzodiazepine antagonism does not provoke a stress response. *Anesthesiology* 1989; 70: 636-639.
 19. Cavagnini F, Invitti C, Pinto M, Maraschini C, Di Landro A, Dubini A, Marelli LP. Effect of acute and repeated administration of gamma-aminobutyric acid (GABA) on growth hormone and prolactin secretion in man. *Acta Endocrinologica* 1980; 93: 149-154.
 20. Steardo L, Iovino M, Monteleone P, Agrusta M, Orio F. Pharmacological evidence for a dual gabaergic regulation of growth hormone release in humans. *Life Sciences* 1986; 39: 979-985.
 21. Briel G, Gylfe E, Hellman B, Neuhoft V. Microdetermination of free amino acids in pancreatic islets isolated from obese hyperglycaemic mice. *Acta Physiologica Scandinavica* 1972; 84: 247-253.
 22. Okada Y, Taniguchi H, Shimada C. High concentration of GABA and high glutamate decarboxylase activity in rat pancreatic islets and human insulinoma. *Science* 1976; 194: 620-622.
 23. Garry D, Sorenson RL, Elde RP, Maley BE, Madsen A. Immunohistochemical colocalisation of GABA and Insulin in β cells of rat islet. *Diabetes* 1986; 35: 1090-1095.
 24. Rorsman P, Berggren P, Bokvist K, Ericson H, Mohler H, Osterson C, Smith PA. Glucose-inhibition of glucagon secretion involves activation of GABA_A receptor chloride channels. *Nature (London)* 1989; 341: 233-236.
 25. Kataoka Y, Gutman Y, Guidotti A, Panula P, Wroblewski J, Cosenza-Murphy D, Wu JY, Costa E. Intrinsic GABAergic system of adrenal chromaffin cells. *Proceedings of the National Academy of Sciences* 1984; 81: 3218-3222.
 26. Al-Khudhairi D, Whitwam JG, Chakrabarti MK, Askito-poulou H, Grundy EM, Powrie S. Haemodynamic effects of midazolam and thiopentone during induction of anaesthesia for coronary artery surgery. *British Journal of Anaesthesia* 1982; 54: 831-834.
 27. Lebowitz PW, Cote ME, Daniels AL, Ramsey FM, Martyn JA, Teplick RS, Davison JK. Comparative cardiovascular effects of midazolam and thiopental in healthy patients. *Anesthesia and Analgesia* 1982; 61: 771-775.

CLONIDINE DECREASES POSTOPERATIVE OXYGEN CONSUMPTION IN PATIENTS RECOVERING FROM GENERAL ANAESTHESIA

L. DELAUNAY, F. BONNET AND P. DUVALDESTIN

SUMMARY

Twenty ASA I patients, undergoing thyroid surgery were allocated randomly to receive at the end of surgery either an isotonic saline solution or clonidine $2 \mu\text{g kg}^{-1}$ i.v. administered over 20 min. Oxygen consumption ($\dot{V}\text{O}_2$) and carbon dioxide production ($\dot{V}\text{CO}_2$) were measured during recovery in patients breathing spontaneously with a head canopy system. Clonidine was found to attenuate the increase in $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ associated with recovery from anaesthesia. The effect of clonidine was associated with a reduction in shivering. Sedative and analgesic properties of clonidine may also contribute to the reduction in metabolic demand during recovery from anaesthesia.

KEY WORDS

Oxygen: oxygen consumption. Recovery. Sympathetic nervous system: clonidine.

Recovery from general anaesthesia is associated with shivering and increase in oxygen consumption ($\dot{V}\text{O}_2$) which may result in hypertension and tachycardia [1-3]. Postoperative shivering is uncomfortable and its haemodynamic consequences may be harmful in patients with coronary artery disease [4]. It has been demonstrated recently that clonidine, an alpha-2 adrenergic agent, attenuated postoperative shivering [5]. The aim of this study was to assess if inhibition of postoperative shivering by clonidine is associated with a reduction in $\dot{V}\text{O}_2$ and carbon dioxide production ($\dot{V}\text{CO}_2$).

PATIENTS AND METHODS

We studied 20 patients ASA physical status I, undergoing thyroid surgery after obtaining informed patient consent and Ethics Committee approval.

Patients with hyper- or hypothyroidism were excluded from the study, in addition to those treated previously by β -adrenergic blocking agents, psychotropic drugs and alpha-2 adrenergic agonist agents. Patients were premedicated orally with lorazepam 1 mg. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and alfentanil $150\text{--}200 \mu\text{g kg}^{-1}$. Vecuronium 0.1 mg kg^{-1} was given to facilitate orotracheal intubation. Ventilation was controlled using a closed system (SA1 Draeger). Anaesthesia was maintained with 50% nitrous oxide and 0.6-1% isoflurane (expired concentration, Multicap Datex) in oxygen and additional bolus doses of alfentanil. At the end of surgery, isoflurane and nitrous oxide were stopped, fresh gas flow was increased to $6\text{--}8 \text{ litre min}^{-1}$ and the anaesthetic breathing system was opened. Patients were allocated randomly to two groups ($n = 10$ each) to receive either an isotonic saline solution (control group) or clonidine $2 \mu\text{g kg}^{-1}$ i.v. injected over 20 min (clonidine group). At the end of the infusion, patients were transferred to the recovery room where measurements began. During the 60 min after arrival in the recovery room $\dot{V}\text{O}_2$, $\dot{V}\text{CO}_2$ and respiratory quotient (RQ) were measured with a head canopy system (Deltatrac metabolic monitor, Datex) while patients were breathing room air spontaneously. Measurements were performed every 1 min and values of $\dot{V}\text{O}_2$, $\dot{V}\text{CO}_2$ and RQ were expressed as the mean value of a 10-min period of measurements. Systemic arterial pressure and heart rate were measured every 10 min in the recovery room (Dinamap) and rectal temperature was noted (rectal sensor: Mon a therm).

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TABLE I. Patient data and clinical events (mean (range or SD))

	Control group (n = 10)	Clonidine group (n = 10)
Sex (M/F)	2/8	0/10
Age (yr)	37 (30–52)	37 (20–49)
Body surface area (m ²)	1.7 (0.2)	1.7 (0.1)
Duration of surgery (min)	78 (17)	78 (16)
Time end of surgery to extubation (min)	13.4 (5.3)	13.3 (3.5)
Rectal temperature in recovery room (°C)	36.5 (0.3)	36.4 (0.4)

In order to assess the validity of $\dot{V}O_2$, $\dot{V}CO_2$ and RQ measurements in postoperative patients, these variables were measured in five healthy volunteers before and 20 min after a 15-min period of inhalation of 50% nitrous oxide in oxygen. $\dot{V}O_2$, $\dot{V}CO_2$ and RQ were identical before and 20 min after nitrous oxide inhalation in these healthy volunteers.

Measurements were performed by an independent observer, unaware of the solution administered. The observer recorded also the occurrence of shivering and evaluated patient sedation and pain on graded scales. *Sedation*: 1 = fully conscious and wake; 2 = drowsy; 3 = mostly sleeping but answering to verbal command; 4 = sleeping and awaked only by tactile stimulation. *Pain*: 1 = no pain; 2 = mild pain; 3 = moderate pain; 4 = severe pain.

Values are expressed as mean (SD). Data were analysed by ANOVA and Scheffé *F* test to show differences at individual time points, and Mann-Whitney test for comparison of patient data. Fisher's exact test was used for comparison of shivering between the two groups. $P < 0.05$ was considered significant.

RESULTS

There was no difference in patient characteristics between the two groups (table I). Duration of surgery, rectal temperature on arrival in the recovery room and time to tracheal extubation were comparable for the two groups. $\dot{V}O_2$ was significantly greater in the control group on arrival in the recovery room compared with the clonidine group and then decreased significantly to reach values similar to those of the clonidine group 60 min later (fig. 1). The changes in $\dot{V}CO_2$ were

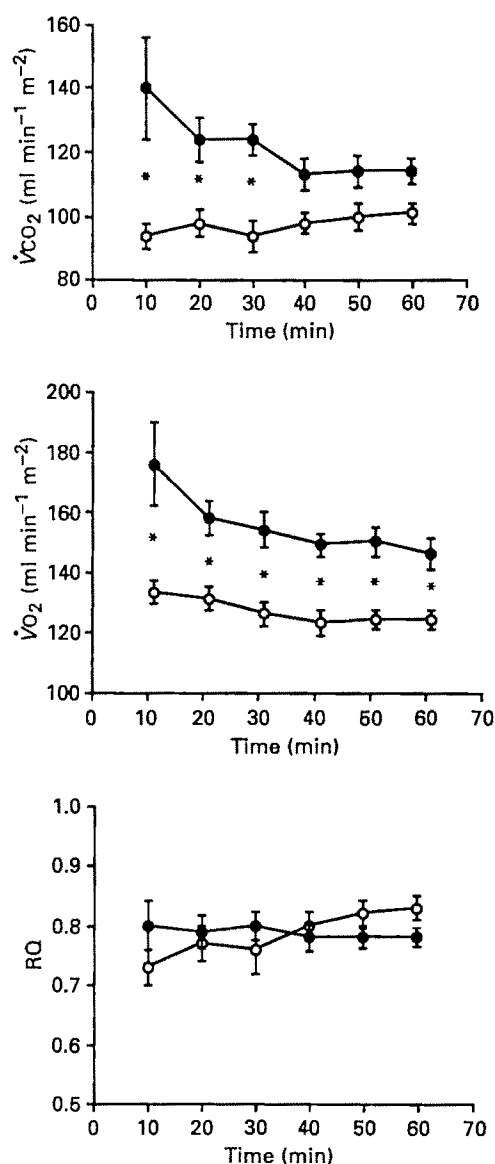


FIG. 1. Changes in $\dot{V}O_2$, $\dot{V}CO_2$ and respiratory quotient (RQ) (mean, SEM) during recovery from anaesthesia. ● = Control group; ○ = clonidine group. Values are expressed as the mean over a 10-min period. * Significant difference ($P < 0.05$) between groups (from the arrival in the recovery room to 30 min later for $\dot{V}CO_2$ and to 60 min later for $\dot{V}O_2$).

similar to those of $\dot{V}O_2$ in the two groups while RQ remained constant throughout the study (fig. 1). Shivering occurred in five patients in the control group, but in only one patient in the clonidine group during the first 15 min of the study (ns). Shivering was considered mild in the placebo group and was minimal in one patient in the

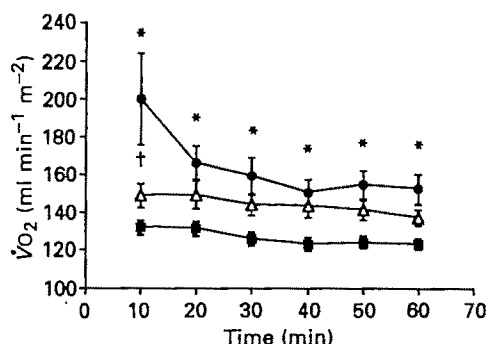


FIG. 2. Changes in $\dot{V}O_2$ (mean, SEM) in shivering (●) and non-shivering (△) patients in the placebo group and non-shivering patients in the clonidine group (■). * Significant difference ($P < 0.05$) between shivering patients in the placebo group ($n = 5$) compared with non-shivering patients in the clonidine group ($n = 9$). † Significant difference ($P < 0.05$) between shivering and non-shivering patients in the placebo group.

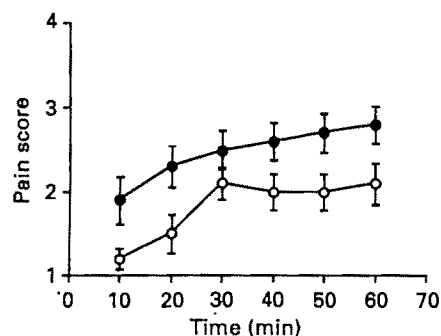
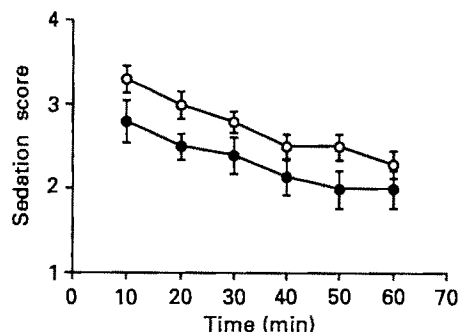


FIG. 3. Changes in the scores (mean, SEM) for sedation and pain in the control (●) and clonidine (○) groups. Differences do not reach statistical significance ($P < 0.1$).

clonidine group. Further analysis of the data revealed that values of $\dot{V}O_2$ were greater in the five patients of the placebo group who shivered compared with the five non-shivering patients in this group or the clonidine group (fig. 2). No significant increase in $\dot{V}O_2$ occurred in the patient

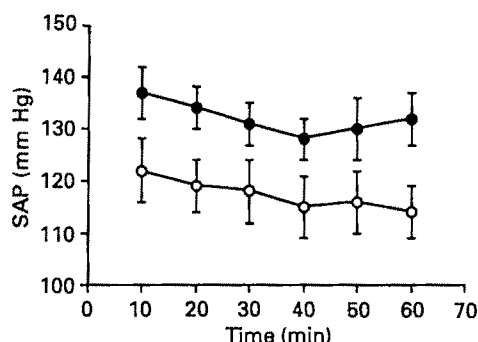
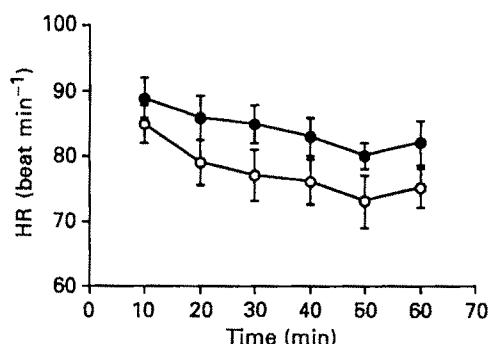


FIG. 4. Changes in mean values of systolic arterial pressure (SAP) and heart rate (HR) (mean, SEM) in the control (●) and clonidine (○) groups. Differences do not reach statistical significance ($P < 0.1$).

of the clonidine group who shivered minimally. Although no significant difference was measured, patients were slightly more sedated but had less pain in the clonidine group (fig. 3), while systolic arterial pressure and heart rate were slightly less in this group (fig. 4).

DISCUSSION

In this study we have observed that clonidine was associated with a reduction in the increase in $\dot{V}O_2$ and $\dot{V}CO_2$ observed commonly during recovery from anaesthesia. This result was associated with a decreased incidence in shivering, as documented previously [4].

Measurement of $\dot{V}O_2$, according to the Haldane equation, assumes that the amount of nitrogen is equal in both inhaled and exhaled gas. Excretion of anaesthetic gas, especially residual nitrous oxide, may therefore lead to an error in measurement of $\dot{V}O_2$ [6]. However, we began measurements at least 20 min after withdrawal of nitrous

oxide when its concentration should be less than 5% of the concentration maintained during anaesthesia (50%)—that is, less than 2.5% [7]. In addition, if there was an error in $\dot{V}O_2$ and $\dot{V}CO_2$ measurements, it should be the same in the two groups of patients, so that a comparison between groups remains valid. Furthermore, measurements performed in healthy volunteers with the Canopy system and the Deltatrac metabolism monitor did not reveal any difference in $\dot{V}O_2$ and $\dot{V}CO_2$ measurements performed before, 20 min, 30 min and 40 min after inhalation of nitrous oxide.

There are conflicting data on the effect of clonidine on postoperative shivering. Flacke and colleagues reported that patients with coronary artery disease who had received clonidine before operation as premedication, and at the end of surgery shivered less commonly than patients in a control group [8]. After administration of clonidine in the recovery room, Quintin and colleagues also reported that the incidence of shivering was decreased [9]. In addition they observed that clonidine reduced the degree of hypertension and tachycardia observed during recovery in a control group and prevented the increase in $\dot{V}O_2$ (calculated from measurements of cardiac output and arterial and mixed venous oxygen contents) [10]. However, it has been reported recently that clonidine failed to change postoperative shivering [11, 12]. Nevertheless, in both these studies calculated or measured $\dot{V}O_2$ was less in patients who received clonidine, especially during the shivering periods, suggesting that the degree of shivering was reduced.

Goldfarb and colleagues also reported that i.v. clonidine induced a rapid decrease in $\dot{V}O_2$ in postoperative patients [12]. Although shivering is described as visible phenomenon, subclinical shivering has been detected using a strain gauge or electromyographic recordings [13, 14]. Difficulties in quantitative analysis of shivering may explain, therefore, the observed discrepancies in these different studies.

In our study, the values of $\dot{V}O_2$ and $\dot{V}CO_2$ were about 40% greater in the control group at the beginning of measurements compared with those in the clonidine group, despite the same temperatures. As shivering is mainly responsible for the increase in $\dot{V}O_2$ and $\dot{V}CO_2$ during recovery from anaesthesia [2, 15], the effect of clonidine on $\dot{V}O_2$ might be related to prevention of shivering. Indeed, values of $\dot{V}O_2$ were comparable in non-

shivering patients in both clonidine and placebo groups. Nevertheless, clonidine reduces sympathetic nervous system activity and plasma catecholamine concentrations [8, 16–18]. This might result in a decrease in whole body metabolism while the decrease in cardiac output related to clonidine [17, 18] leads to a decrease in myocardial oxygen consumption. These effects may combine in reducing the $\dot{V}O_2$ and $\dot{V}CO_2$ observed after administration of clonidine. Furthermore, the analgesic effect of clonidine observed previously in postoperative patients [19–21] might account partly for the reduction in $\dot{V}O_2$, as Muneyuki and colleagues have demonstrated that reduction of pain in the postoperative period caused a 7–8% decrease in $\dot{V}O_2$ [22].

REFERENCES

1. Bay J, Nunn JF, Prys-Robert C. Factors influencing arterial PO_2 during recovery from anaesthesia. *British Journal of Anaesthesia* 1968; 40: 398–407.
2. Ciofolo MJ, Clergue F, Devilliers C, Ben Ammar M, Viars P. Changes in ventilation, oxygen uptake and carbon dioxide output during recovery from isoflurane anaesthesia. *Anesthesiology* 1989; 70: 737–741.
3. Rodriguez JL, Weissman C, Damask MC, Askanazi J, Hyman AI, Kinney JM. Morphine and postoperative rewarming in critically ill patients. *Circulation* 1983; 68: 1238–1246.
4. Coriat P, Mundler O, Bousseau D, Fauchet M, Rous AC, Echter E, Viars P. Response of left ventricular ejection fraction to recovery from general anaesthesia: measurement by gated radio-nuclide angiography. *Anesthesia and Analgesia* 1986; 65: 593–600.
5. Goldfarb G, Ang ET, Debaene B, Khon S, Jolis P. Effect of clonidine on postoperative shivering in man. A double-blind study. *Anesthesiology* 1989; 71: A650.
6. Aukburg SJ, Geer RT, Wollman H, Neufeld GR. Errors in measurement of oxygen uptake due to anesthetic gases. *Anesthesiology* 1985; 62: 54–59.
7. Stoetling RK, Eger EI. The effects of ventilation and anesthetic solubility on recovery from anaesthesia. An *in vivo* and analog analysis before and after equilibration. *Anesthesiology* 1969; 30: 290–396.
8. Flacke JW, Bloor BC, Flacke WE, Wong D, Dazza S, Stead SW, Laks H. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; 67: 11–19.
9. Quintin L, Roudot F, Roux C, Macquin I, Basmaciogullari A, Guyene T, Vanbourdolle M, Bonnet F, Ghignone M. Effect of clonidine on the circulation and vasoactive hormones after aortic surgery. *British Journal of Anaesthesia* 1991; 66: 108–115.
10. Quintin L, Viale JP, Annat G, Hoen JP, Butin E, Cottet-Eymard JM, Levron JC, Bassery D, Motin J. Oxygen

- uptake after major abdominal surgery: Effect of clonidine. *Anesthesiology* 1991; 74: 236-241.
11. Bernard JM, Hommeril JL, Passuti N, Pinaud M. IV clonidine fails to inhibit postoperative shivering. *Anesthesiology* 1990; 73: A240.
 12. Goldfarb G, Ang ET, Debaene B, Chlim S, Jolis P. Effect of clonidine on postoperative oxygen consumption in humans. *Anesthesiology* 1990; 73: A317.
 13. Sessler DI, Forael D, Pozos RS, Pozos M, Rubinstein EM. Spontaneous postanesthetic tremor does not resemble thermoregulatory shivering. *Anesthesiology* 1988; 68: 843-850.
 14. Pflug AE, Ashein GM, Foster C, Martin RW. Prevention of postanesthesia shivering. *Canadian Anaesthetists Society Journal* 1978; 525: 43-49.
 15. Roe CR, Goldberg MJ, Blair CS, Kinney JM. The influence of body temperature on early postoperative oxygen consumption. *Surgery* 1966; 60: 85-92.
 16. Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. *Anesthesiology* 1987; 67: 3-10.
 17. Laubie M, Schmitt H. Influence of autonomic blockade on the reduction in myocardial performance produced by clonidine. *Clinical Pharmacokinetics* 1988; 14: 287-310.
 18. Nayler WG, Price JM, Stone J, Lowe TC. Further observations on the cardiovascular effects of ST-155. *Journal of Pharmacology and Experimental Therapeutics* 1969; 166: 364-373.
 19. Bernard JM, Lechevalier T, Pinaud M, Passuti N. Postoperative analgesia by iv clonidine. *Anesthesiology* 1989; 71: A154.
 20. Bonnet F, Boico O, Rostaing S, Loriferne JF, Saada M. Clonidine induced analgesia in postoperative patients: epidural versus intramuscular administration. *Anesthesiology* 1990; 72: 25-29.
 21. Bonnet F, Boico O, Rostaing S, Saada M, Loriferne JF, Touboul C, Abhay K, Ghignone M. Postoperative analgesia with extradural clonidine. *British Journal of Anaesthesia* 1989; 63: 465-469.
 22. Muneyuki M, Ueda Y, Urabe N, Takeshita H, Inamoto A. Postoperative pain relief and respiratory function in man. Comparison between intermittent intravenous injections of meperidine and continuous lumbar epidural analgesia. *Anesthesiology* 1968; 29: 304-313.

A COMPARISON OF DEXMEDETOMIDINE, AN α_2 -ADRENOCEPTOR AGONIST, AND MIDAZOLAM AS I.M. PREMEDICATION FOR MINOR GYNAECOLOGICAL SURGERY

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SUMMARY

The effects of i.m. dexmedetomidine $1.0 \mu\text{g kg}^{-1}$, a new α_2 -adrenoceptor agonist, were compared with those of i.m. midazolam 0.08 mg kg^{-1} and placebo on vigilance, anaesthetic requirements, haemodynamic state and plasma catecholamine concentrations in a double-blind placebo-controlled study in 107 healthy (ASA physical status I-II) women undergoing cervical dilatation and uterine curettage. The premedicants were administered i.m. 60 min before induction of anaesthesia with thiopentone. Nitrous oxide 70% in oxygen and thiopentone were used for maintenance. Both premedicants were tolerated well and no serious haemodynamic or other adverse events occurred. Dexmedetomidine caused moderate reductions in arterial pressure (maximally by 20%) and heart rate (maximally by 15%). Atropine was administered to two dexmedetomidine-premedicated patients because of bradycardia $< 45 \text{ beat min}^{-1}$. Both premedicants decreased the plasma concentrations of nor-adrenaline by about 50%, but only dexmedetomidine attenuated the catecholamine response to anaesthesia and surgery. The thiopentone requirements were decreased significantly ($P = 0.003$) by both dexmedetomidine (17%) and midazolam (19%). Recovery times were 11.3 (SD 4.2) min after midazolam, 8.5 (5.2) min after dexmedetomidine and 5.6 (11.4) min after placebo ($P = 0.006$ between midazolam and placebo groups, other differences ns).

KEY WORDS

Premedication: dexmedetomidine, midazolam. Surgery: gynaecological.

α_2 -adrenoceptor agonists have aroused increasing interest as a potentially useful class of drugs in anaesthesia [1, 2]. They cause sedation and drying of the mouth, potentiate the effects of general anaesthetic agents and attenuate sympathoadrenal responses to noxious stimuli during anaesthesia and surgery, thus providing improved haemodynamic, metabolic and hormonal stability [3].

Dexmedetomidine is a new lipophilic imidazole derivative [4] with high affinity for α_2 -adrenoceptors [5]. Its most prominent clinical effects are sedation and dry mouth. In animal studies it has been shown to possess potent anaesthetic properties [6]. In previous studies [7, 8] we have reported the effects of a single i.v. injection of dexmedetomidine in minor gynaecological surgery: it reduced requirement for thiopentone by up to 55%, with moderate reductions (10-20%) in arterial pressure and heart rate and up to 75% decreases in plasma concentrations of nor-adrenaline.

In order to study a clinically more convenient route of administration for premedication, we have compared the effects of i.m. dexmedeto-

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midine with midazolam and placebo on vigilance, anaesthetic requirements, and haemodynamic state during minor gynaecological surgery under thiopentone-nitrous oxide anaesthesia.

MATERIALS AND METHODS

We studied 108 non-pregnant women undergoing cervical dilatation and uterine curettage (D&C) (ASA physical status I-II, ages 45.8 (SD 6.3) yr, weight 65.8 (10.2) kg (table I)). The patients were admitted to hospital only for gynaecological reasons (abnormal bleeding) and were not receiving any medication. The study was approved by the Ethics Committee of Turku University Hospital and the Finnish National Board of Health. Written informed consent was obtained from each patient.

The patients were allocated randomly to receive i.m. either dexmedetomidine $1.0 \mu\text{g kg}^{-1}$ ($n = 35$; one patient from the intended 36 was excluded because of technical difficulties in the operating unit after allocation to group but before treatment), midazolam 0.08 mg kg^{-1} ($n = 36$) or an equal volume (1–2 ml) of 0.9% saline ($n = 36$). The study was conducted in a double-blind fashion, with an independent nurse who prepared the drug solutions in coded injection syringes and took no further part in the study.

Patients entered hospital 1 day before scheduled surgery. After fasting overnight and at least 60 min of rest in the supine position, the patients were transferred to the operating unit at least 75 min before D&C. Our studies took place between 09:00 and 14:00 and were performed in a quiet, dimly lit room with a constant light before

and after D&C, which was performed in a standard operating theatre. Upon arrival in the operating unit, continuous monitoring of the electrocardiogram and heart rate (HR) and non-invasive recording of systolic (SAP) and diastolic (DAP) pressure at 15-min intervals were started with an automated oscillometric device (Nippon Colin 203Y, Tokyo, Japan). The anaesthetist was not aware of the results of these measurements, which were recorded by an independent research nurse. An antecubital vein on the left arm was cannulated for administration of the anaesthetic (2.5% thiopentone) and collection of blood samples. Blood samples were collected 5 min before and 45 min after premedication, and at the end of D&C and 30, 60 and 180 min after recovery from anaesthesia for measurement of plasma concentrations of noradrenaline and adrenaline from the first 48 patients ($n = 16$ each group).

Dexmedetomidine, midazolam or saline was administered i.m. in the left vastus lateralis muscle 60 min before induction of anaesthesia. Anaesthesia was induced with thiopentone in small increments of 25–50 mg at 10–15 s intervals and the induction dose (enough to suppress the eyelash reflex) was recorded [9]. Anaesthesia was maintained with 70% nitrous oxide in oxygen 9 litre min^{-1} via a modified Mapleson F system. If spontaneous movements occurred, additional bolus doses of thiopentone 25 mg were given. The time needed to regain consciousness (i.e. when the patient opened her eyes at verbal command) after the termination of nitrous oxide was recorded.

After the D&C and recovery from anaesthesia, the patients were observed and tested for 3 h. Impairment of vigilance was assessed objectively with the Maddox wing (which measures the balance of the extraocular musculature [10]) and the critical flicker fusion test [11]. Visual analogue scales (VAS) (patient marking on a 100-mm ungraded horizontal line with opposite extremes at each end) were used to obtain subjective estimates [12] of fear, anxiety, dizziness, tiredness, dryness of mouth, nausea, headache and pain. The patients were familiarized with the use of the Maddox wing and critical flicker fusion apparatus and the VAS on the day before surgery, and they were urged to report any possibly drug-related subjective sensations immediately. VAS and a questionnaire to record other subjective sensations were repeated 15 and 1 min before, and 15, 30 and 45 min after premedication and 10, 30, 60, 120 and 180 min after recovery from anaesthesia.

TABLE I. Patient and operation characteristics (mean (range or SD))

Drug	Age (yr)	Weight (kg)	Duration of surgery (min)
Saline ($n = 36$)	46.6 (32–59)	66.2 (12.1)	6.6 (2.5)
Dexmedetomidine 1.0 mg kg^{-1} ($n = 35$)	46.7 (30–59)	67.3 (9.8)	6.9 (2.7)
Midazolam 0.08 mg kg^{-1} ($n = 36$)	44.1 (33–57)	64.0 (8.6)	6.6 (3.4)
One-way ANOVA			
F	2.1	1.0	0.1
P	0.133	0.374	0.916

A question on intraoperative awareness was included in the questionnaire after recovery from anaesthesia.

Blood for the chemical determinations was collected into chilled polypropylene tubes with K_2 EDTA and stored in ice until centrifuged within 2 h at 0–4 °C. The plasma samples were stored at –70 °C until assayed.

Plasma concentrations of catecholamines were measured using high pressure liquid chromatography with electrochemical detection (HPLC–EC) [13]. The reproducibility of the assay was tested using pooled plasma samples from previous clinical studies, and the resulting intra-assay coefficients of variation were less than 2% for noradrenaline, and approximately 10% for adrenaline in the relevant concentration ranges. All samples from one experimental session were analysed in one assay.

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) or either analysis of variance or analysis of covariance (ANCOVA) for repeated measurements with one between factor (drug) and one within factor (time). The ANOVA for repeated measurements on VAS, the Maddox wing and critical flicker fusion data were performed over two periods of time, separated by the surgical procedure. Noradrenaline and adrenaline data were analysed with ANOVA for repeated measurements over the whole observation period. The data on VAS, noradrenaline and adrenaline were log-transformed in order to achieve normality of the residuals in ANOVA for repeated measurements. Haemodynamic data were analysed over three periods of time: from the beginning of the study until induction of anaesthesia (ANOVA for repeated measurements), the time during the surgical procedure (ANCOVA for repeated measurements with Wald-type asymptomatic chi-square testing, because of incomplete data), and from the end of the operation until the end of the observation period (ANOVA for repeated measurements). Greenhouse–Geisser adjusted probability values were used when pooled orthogonal components showed non-sphericity. When a statistically significant drug effect or drug $\times$ time interaction was found, the analysis was continued by calculating contrasts for each pair of drugs using the Bonferroni correction for multiple comparisons [14]. $P < 0.05$ was con-

sidered statistically significant. The statistical analysis was performed using BMDP (BMDP Statistical Software Inc, CA, U.S.A.) and SAS (SAS Institute Inc., NC, U.S.A.) statistical programs. The results in the text are given as means (SD).

RESULTS

The three groups were equal in weight, age and duration of surgery (table I). Dexmedetomidine and midazolam were tolerated well and none of the patients experienced local irritation at the injection site. However, two patients in the dexmedetomidine group received atropine 0.5 mg i.v. because of sinus bradycardia < 45 beat min^{-1} , one during D&C (baseline HR 55 beat min^{-1}) and the other (baseline HR 57 beat min^{-1}) approximately 60 min after recovery. In both patients, bradycardia responded to atropine. None of the subjects reported awareness during anaesthesia.

The patients who had received midazolam were subjectively more tired before induction of anaesthesia than those in the placebo group, but there were no significant differences between the dexmedetomidine and midazolam groups or be-

TABLE II. Analysis of variance for repeated measurements with drug (dexmedetomidine, midazolam and placebo) as between factor and time as within factor on subjective tiredness, Maddox wing readings and critical flicker fusion frequency. For comparisons between groups, see figure 1

	Factor 1 (drug)	Factor 2 (time)	Inter- action
Beginning of study to induction of anaesthesia			
Tiredness			
F	7.4	70.1	2.7
P	0.001	< 0.001	0.028
Maddox wing			
F	4.9	13.0	14.7
P	0.010	< 0.001	< 0.001
Critical flicker fusion			
F	0.2	6.3	3.1
P	0.835	0.014	0.051
End D&C until end of study			
Tiredness			
F	5.4	61.5	3.2
P	0.006	< 0.001	0.014
Maddox wing			
F	2.8	77.6	1.0
P	0.066	< 0.001	0.408
Critical flicker fusion			
F	0.02	2.6	0.5
P	0.984	0.084	0.729

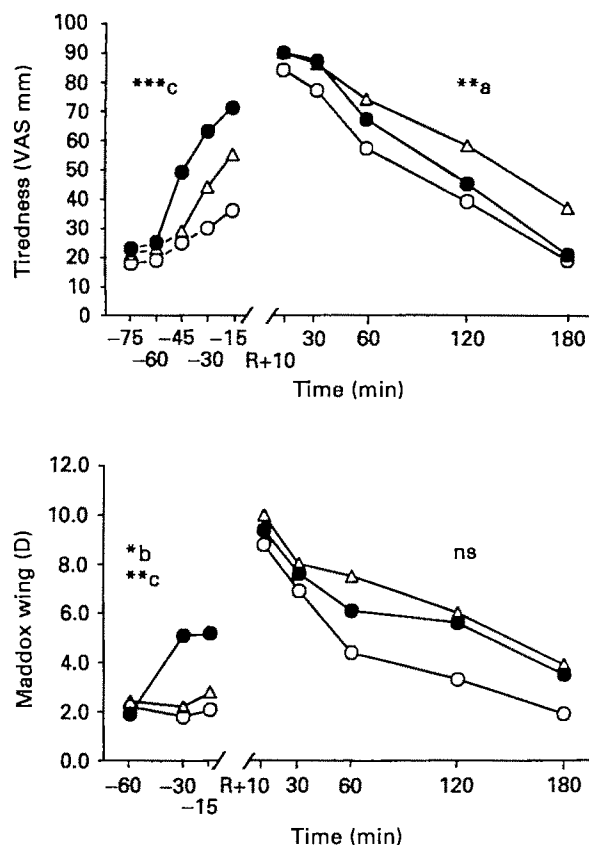


FIG. 1. Mean VAS scores for subjectively estimated tiredness and the Maddox wing readings in diopters (D) after saline (○), midazolam 0.08 mg kg⁻¹ (●) or dexmedetomidine 1.0 µg kg⁻¹ (△). R = Recovery from anaesthesia. Significant differences: **P* < 0.05; ***P* < 0.01; ****P* < 0.001 (a = dexmedetomidine vs placebo; b = dexmedetomidine vs midazolam; c = midazolam vs placebo).

tween the dexmedetomidine and placebo groups in sedation at that time (table II, fig. 1) After D&C, patients in the dexmedetomidine group were subjectively more tired than those in the placebo group, but no more tired than those in the midazolam group until the end of the study (table II, fig. 1). Patients in the midazolam group were not significantly more tired than those in the placebo group after D&C (fig. 1).

The Maddox wing readings revealed a statistically significant difference between the midazolam and dexmedetomidine groups and between the midazolam and placebo groups, but not between the dexmedetomidine and placebo groups before induction of anaesthesia (table II, fig. 1). There were no significant differences between the groups in critical flicker fusion

TABLE III. The mean (SD) required thiopentone doses after saline placebo, dexmedetomidine 1.0 µg kg⁻¹ and midazolam 0.08 mg kg⁻¹ for D&C

Drug	Induction dose (mg)	Maintenance dose (mg)	Total dose (mg)
Saline (n = 36)	300 (82)	122 (74)	422 (98)
Dexmedetomidine (n = 35)	241 (68)	109 (66)	350 (93)
Midazolam (n = 36)	210 (74)	133 (79)	343 (121)
ANOVA			
<i>F</i>	13.3	0.9	6.1
<i>P</i>	< 0.001	0.409	0.003

TABLE IV. Analysis of variance and covariance for repeated measurements with drug (dexmedetomidine, midazolam and placebo) as between factor and time as within factor over three different time periods on SAP, DAP and HR. For comparisons between groups, see figure 2

	Factor 1 (drug)	Factor 2 (time)	Inter- action
Beginning of study to induction of anaesthesia (ANOVA)			
SAP			
<i>F</i>	8.4	39.4	3.4
<i>P</i>	< 0.001	0.008	0.004
DAP			
<i>F</i>	3.6	13.2	1.0
<i>P</i>	0.032	< 0.001	0.395
HR			
<i>F</i>	1.0	1.9	0.7
<i>P</i>	0.357	0.143	0.614
During D&C (ANCOVA)			
SAP			
χ^2	11.0	80.8	2.7
<i>P</i>	0.004	< 0.001	0.610
DAP			
χ^2	4.6	73.9	2.9
<i>P</i>	0.103	< 0.001	0.582
HR			
χ^2	14.9	5.9	7.7
<i>P</i>	0.001	0.054	0.104
End of operation to end of the study (ANOVA)			
SAP			
<i>F</i>	17.6	31.0	1.5
<i>P</i>	< 0.001	< 0.001	0.123
DAP			
<i>F</i>	18.7	31.0	2.1
<i>P</i>	< 0.001	< 0.001	0.007
HR			
<i>F</i>	11.9	28.0	1.0
<i>P</i>	< 0.001	< 0.001	0.478

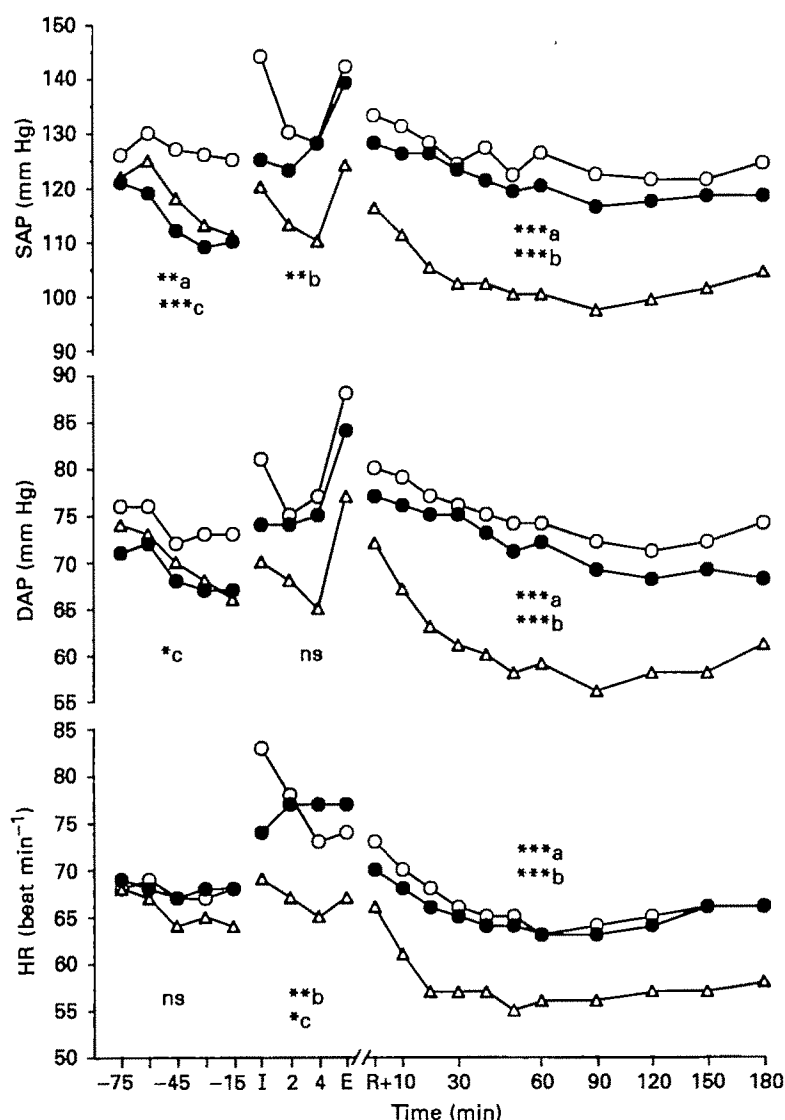


FIG. 2. Mean values of SAP, DAP and HR. Symbols as in figure 1. I = Induction of anaesthesia; E = end of the operation; R = recovery from anaesthesia. (Note different time scale during anaesthesia.)

frequency before induction of anaesthesia or in critical flicker fusion frequency and the Maddox wing readings after D&C (table II, fig. 1).

There were no clinically significant differences between the groups in subjective assessment of fear, anxiety, dizziness, dryness of mouth, nausea, headache or pain before premedication, after the premedication but before D&C, or after D&C. The average values for VAS were small and remained less than 15 mm in each group throughout the study period at all assessments. Six

patients (two in each group) required analgesic supplementation after D&C (oxycodone 5 mg i.v. and 5 mg i.m.).

The thiopentone dose needed for induction of anaesthesia was significantly less in the dexmedetomidine (241 (68) mg) and midazolam groups (210 (74) mg) than in the placebo group (300 (82) mg; $P = 0.004$ for dexmedetomidine *vs* placebo and $P < 0.001$ for midazolam *vs* placebo in pairwise comparisons), but the difference between the two first groups was not significant in

a pairwise comparison. The total dose was decreased similarly: $P = 0.016$ for dexmedetomidine *vs* placebo, $P = 0.006$ for midazolam *vs* placebo, and no significant difference between dexmedetomidine and midazolam in pairwise comparisons. There were no differences in the maintenance dose of thiopentone ($P = 0.409$ in one-way ANOVA) (table III).

There were significant differences between the groups in recovery time ($P = 0.008$ in one-way ANOVA): the mean time needed for recovery after the termination of nitrous oxide was twice as long in those patients pretreated with midazolam (11.3 (4.2) min) than in those pretreated with placebo (5.6 (11.4) min) ($P = 0.006$ in pairwise comparisons). The mean recovery time was 8.2 (5.2) min in the dexmedetomidine group (not statistically different from those of the two other groups).

SAP was significantly lower after dexmedetomidine and midazolam premedication than after placebo treatment before induction of anaesthesia (table IV, fig. 2). During D&C the patients in the dexmedetomidine group had significantly smaller SAP than those in the midazolam group. SAP was lower in the dexmedetomidine-treated patients than in those in the two other groups after D&C until the end of the study.

The patients in the midazolam group had significantly lower DAP than those in the placebo group before induction of anaesthesia, but there were no significant differences between the groups during D&C (table IV, fig. 2). After D&C, patients in the dexmedetomidine group had significantly lower DAP than those in the other two groups.

There were no significant differences between the groups in HR before induction of anaesthesia (table IV, fig. 2). During D&C and until the end of the study, HR was constantly significantly less in the dexmedetomidine group than in the two other groups.

Plasma concentrations of noradrenaline and adrenaline were significantly less in the dexmedetomidine group than in the two other groups ($P < 0.001$ in overall ANOVA) (fig. 3). There was a parallel decline in the plasma concentrations of noradrenaline after dexmedetomidine and midazolam, while no change occurred in the placebo group. An increase in plasma concentrations of noradrenaline after D&C occurred only in the placebo and midazolam groups. Similarly, an increase in the plasma concentrations of adren-

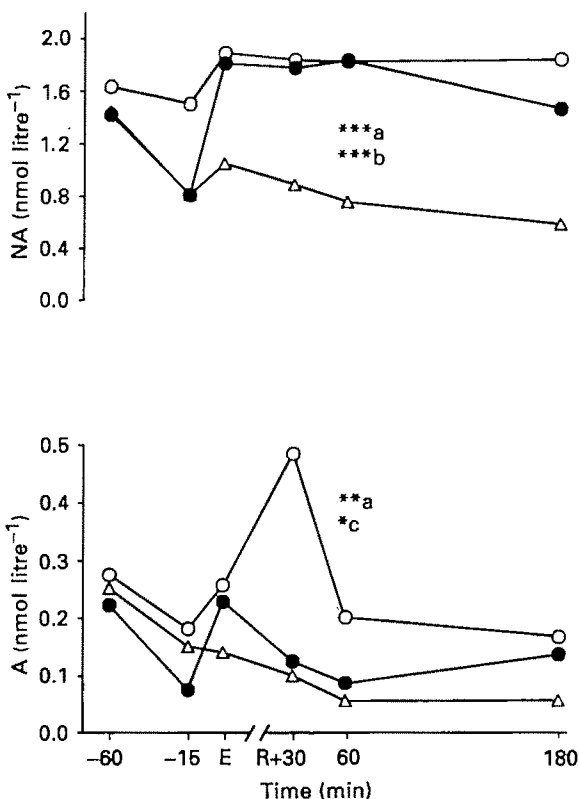


FIG. 3. Mean plasma concentrations of noradrenaline (NA) and adrenaline (A) ($n = 16$ each group). Symbols as in figure 1. E = end of the operation; R = recovery from anaesthesia.

aline after D&C occurred in the placebo and midazolam groups only ($P = 0.015$ in overall ANOVA) (fig. 3).

DISCUSSION

I.m. administration of premedication is a convenient route of drug delivery in adults. Most premedicants are absorbed rapidly and reliably after i.m. administration, thus providing a rapid onset of action [15]. Midazolam is absorbed and eliminated rapidly after i.m. injection: t_{max} is approximately 30 min and $T_{1/2}$ approximately 1.5 h [16, 17]. Dexmedetomidine is absorbed less rapidly than midazolam after i.m. administration and has a t_{max} of approximately 1.5 h and $T_{1/2}$ of approximately 2 h in the relevant dose range [data on file, Farnos Group Ltd, Turku, Finland].

As expected from the pharmacokinetic data and previous clinical reports [16, 18, 19], the sedative effects of midazolam in the present study were noted 15 min after injection of drug, indicating

rapid absorption of drug. I.m. midazolam produced satisfactory sedation before surgery. This was seen both in the subjective assessment and in the Maddox wing readings which were used as an objective measure of vigilance. Although there was some increase in the subjective assessment of tiredness after dexmedetomidine, it was not statistically significantly different from that after placebo. Thus the dexmedetomidine dose may have been too small or the drug may have had too slow an onset of action to produce adequate sedation during the 60-min observation period before surgery (fig. 1).

Benzodiazepines effectively reduce preoperative anxiety [15]. In a previous study, premedication with clonidine 300 µg by mouth significantly decreased preoperative anxiety [20]. In the present investigation, however, there was no effect on anxiety after either dexmedetomidine or midazolam. A preoperative visit by the anaesthetist (performed during the present study) is known to reduce preoperative anxiety effectively [21]. Moreover, D&C is a minor gynaecological operation, and patients in the ward rarely show apprehension. Consequently, the initial anxiety, as assessed by the patients themselves, was minimal on arrival in the operating unit; thus it was difficult to demonstrate anxiolysis after premedication.

The amount of thiopentone required for the induction of anaesthesia was decreased after dexmedetomidine and midazolam. Clonidine has been shown to decrease MAC for volatile anaesthetics and opioid requirements during coronary bypass surgery [22, 23], and to reduce the induction dose of thiopentone [24], propofol [25] and methohexitone [20]. We have previously demonstrated reductions of up to 55% in thiopentone requirement after i.v. dexmedetomidine in minor gynaecological surgery [7, 8]. Similarly, midazolam premedication decreases MAC for halothane when used as an i.v. premedicant [15]. The reduction in anaesthetic requirements produced by α_2 -adrenoceptor agonists is believed to be caused by actions on both pre- and post-synaptic inhibitory α_2 -adrenoceptors in the central nervous system [26], whereas the hypnotic effects of benzodiazepines are related to facilitation of GABAergic inhibitory neurotransmission in the central nervous system [27].

In a previous investigation, oral premedication with clonidine prolonged recovery times during total i.v. propofol anaesthesia for body surface

surgery [25]. In the present study, the time needed to regain consciousness after anaesthesia was increased significantly after midazolam but not after dexmedetomidine. In contrast, in spite of the decreased thiopentone requirements, the patients in the dexmedetomidine group were subjectively more tired at the end of the observation period (4 h after the drug administration) than those in the two other groups (fig. 1). Thus, although there were no significant differences in the objective evaluation of vigilance, the increased tiredness after dexmedetomidine and the prolonged recovery time after midazolam indicate that both drugs have undesirably long sedative actions when administered i.m. in the doses used (dexmedetomidine 1.0 µg kg⁻¹ and midazolam 0.08 mg kg⁻¹).

In the present study, the plasma concentrations of noradrenaline decreased initially, by approximately 50%, after dexmedetomidine and midazolam, but only dexmedetomidine prevented the increase in the plasma concentrations of noradrenaline caused by anaesthesia and surgery (fig. 3). The small increase in the plasma concentrations of adrenaline, which occurred in the placebo and midazolam groups after anaesthesia and surgery, was attenuated also only in the dexmedetomidine-pretreated patients (fig. 3). The reduction in plasma concentrations of noradrenaline produced by dexmedetomidine is caused by inhibition of the release of noradrenaline from sympathetic nerve endings [28]. The activation of inhibitory α_2 -adrenoceptors by dexmedetomidine seems to prevent the stress-induced increases in plasma concentrations of noradrenaline and adrenaline. Benzodiazepines have also been shown previously to reduce neuronal release of noradrenaline and plasma concentrations of noradrenaline [29, 30]. However, midazolam did not inhibit the stress-induced increase in plasma concentrations of catecholamines in the present study.

The moderate reductions in arterial pressure (15–20%) and heart rate (10–15%) after dexmedetomidine found in the present study are consistent with our previous observations [7, 8] and are related to the decline in sympathetic nervous activity [31]. Two dexmedetomidine-pretreated patients required atropine for sinus bradycardia, which indicates that an anticholinergic agent may be needed with i.m. dexmedetomidine, especially if the patient has a low baseline HR.

ACKNOWLEDGEMENT

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REFERENCES

- Longnecker DE. Alpine anesthesia: Can pretreatment with clonidine decrease the peaks and valleys? *Anesthesiology* 1987; 67: 1-2.
- Hamilton WK. Fashion, Darwin, and anesthetics as poisons. *Anesthesiology* 1988; 69: 811-812.
- Bloor BC. Clonidine and other α_2 -adrenergic agonists: An important new drug class for the peri-operative period. *Seminars in Anesthesia* 1988; 7: 170-177.
- Savola JM, Ruskoaho H, Puurunen J, Salonen JS, Kärki NT. Evidence for medetomidine as a selective and potent agonist of α_2 -adrenoceptors. *Journal of Autonomic Pharmacology* 1986; 5: 275-284.
- Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an α_2 -adrenoceptor agonist. *European Journal of Pharmacology* 1988; 150: 9-14.
- Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central α_2 -adrenoceptors. *Anesthesiology* 1989; 71: 75-79.
- Aantaa RE, Kanto JH, Scheinin M, Kallio AMI, Scheinin H. Dexmedetomidine premedication for minor gynecologic surgery. *Anesthesia and Analgesia* 1990; 70: 407-413.
- Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an α_2 -adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology* 1990; 73: 230-235.
- Dundee JW, Hassard TH, McGowan WAW, Henshaw J. The "induction" dose of thiopentone. A method of study and preliminary illustrative results. *Anaesthesia* 1982; 37: 1176-1184.
- Hannington-Kiff JG. Measurement of recovery from outpatient general anaesthesia with a simple ocular test. *British Medical Journal* 1970; 3: 132-135.
- Smith JM, Misiak H. Critical flicker frequency (CFF) and psychotropic drugs in normal human subjects—a review. *Psychopharmacology* 1976; 47: 175-182.
- Maxwell C. Sensitivity and accuracy of the visual analogue scale: a psycho-physical classroom experiment. *British Journal of Clinical Pharmacology* 1978; 6: 15-24.
- Scheinin M, Koulou M, Laurikainen E, Allonen H. Hypokalaemia and other non-bronchial effects of inhaled fenoterol and salbutamol: a placebo-controlled dose-response study in healthy volunteers. *British Journal of Clinical Pharmacology* 1987; 24: 645-653.
- Looney SW, Stanley WB. Exploratory repeated measures analysis for two or more groups. *American Statistician* 1989; 43: 220-225.
- White PF. Pharmacologic and clinical aspects of pre-operative medication. *Anesthesia and Analgesia* 1986; 65: 963-974.
- Avram MJ, Fragen RJ, Caldwell NJ. Dose-finding and pharmacokinetic study of intramuscular midazolam. *Journal of Clinical Pharmacology* 1987; 27: 314-317.
- Holazo AA, Winkler MB, Patel HI. Effects of age, gender and oral contraceptives on intramuscular midazolam pharmacokinetics. *Journal of Clinical Pharmacology* 1988; 28: 1040-1045.
- Vinik HR, Reves JG, Wright D. Premedication with intramuscular midazolam: a prospective randomized double-blind controlled study. *Anesthesia and Analgesia* 1982; 61: 933-937.
- Shafer A, White PF, Urquhart ML, Doze VA. Outpatient premedication: Use of midazolam and opioid analgesics. *Anesthesiology* 1989; 71: 495-501.
- Wright PMC, Carabine UA, McClune S, Orr DA, Moore J. Preanaesthetic medication with clonidine. *British Journal of Anaesthesia* 1990; 65: 628-632.
- Egbert LD, Battit GE, Turndorf H, Beecher HK. The value of the preoperative visit by an anesthetist. *Journal of the American Medical Association* 1963; 185: 553-555.
- Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. *Anesthesiology* 1986; 64: 36-42.
- Flacke JW, Bloor BC, Flacke WE, Wong D, Dazza S, Stead SW, Laks H. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; 67: 11-19.
- Orko R, Pouttu J, Ghignone M, Rosenberg PH. Effect of clonidine on haemodynamic responses to endotracheal intubation and on gastric acidity. *Acta Anaesthesiologica Scandinavica* 1987; 31: 325-329.
- Richards MJ, Skues MA, Jarvis AP, Prys-Roberts C. Total i.v. anaesthesia with propofol and alfentanil: dose requirements for propofol and the effect of premedication with clonidine. *British Journal of Anaesthesia* 1990; 65: 157-163.
- Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through postsynaptic α_2 -adrenergic receptor. *Anesthesiology* 1988; 69: 818-823.
- Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985; 62: 310-324.
- Langer SZ. Presynaptic regulation of the release of catecholamines. *Pharmacological Reviews* 1981; 32: 337-362.
- Hossain V, Maling TJB, Hamilton CA, Reid JL, Dollery CT. Sedative and cardiovascular effects of clonidine and nitrazepam. *Clinical Pharmacology and Therapeutics* 1980; 28: 167-176.
- Valtonen M, Salonen M, Forssell H, Scheinin M, Viinamäki O. Propofol infusion for sedation in outpatient oral surgery. *Anaesthesia* 1989; 44: 730-734.
- Scheinin M, Kallio A, Koulou M, Viikari J, Scheinin H. Sedative and cardiovascular effects of medetomidine, a novel selective α_2 -adrenoceptor agonist in healthy volunteers. *British Journal of Clinical Pharmacology* 1987; 24: 443-451.

EFFECTS OF ADENOSINE TRIPHOSPHATE ON THE CARDIOVASCULAR RESPONSE TO TRACHEAL INTUBATION

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SUMMARY

Laryngoscopy and tracheal intubation often cause hypertension and tachycardia, which may be exaggerated during rapid-sequence induction of anaesthesia. The efficacy of adenosine triphosphate (ATP) in attenuating this response was studied in patients receiving ATP 0.05 mg kg⁻¹ or 0.1 mg kg⁻¹ simultaneously with the start of laryngoscopy. These data were compared with those for a control group receiving saline. Each group consisted of 10 patients undergoing elective surgery. Anaesthesia was induced with thiopentone 5 mg kg⁻¹ i.v. and tracheal intubation was facilitated with vecuronium 0.2 mg kg⁻¹ i.v. During anaesthesia, ventilation was assisted or controlled with 1% enflurane and 50% nitrous oxide in oxygen. Patients receiving saline showed a significant increase in mean arterial pressure and rate-pressure product associated with tracheal intubation. These increases after tracheal intubation were reduced in ATP-treated patients compared with those of the control group ($P < 0.05$). The data suggest that a bolus injection of ATP is a simple, practical and effective method for attenuating the hypertensive response to laryngoscopy and tracheal intubation.

KEY WORDS

Arterial pressure; adenosine triphosphate. Complications: hypertension. Intubation, tracheal: haemodynamic response.

Laryngoscopy and tracheal intubation often provoke a marked sympathetic response, which may result in hypertension, tachycardia and arrhythmia [1-3]. Such cardiovascular disturbances, although transient, may be dangerous in some patients, particularly those suffering from myocardial or cerebrovascular disease. Several phar-

macological attempts have been made to control this stress response to laryngoscopy and intubation [1]. They include low doses of fentanyl, local anaesthetic, and α - or β -adrenergic blocking agents [1]. Vasodilating agents such as sodium nitroprusside [4], nitroglycerin [5], isosorbide dinitrate [6] and prostaglandin E₁ [7] have also been shown to be effective for this purpose. The present study was designed to evaluate the efficacy of a single rapid administration of adenosine triphosphate (ATP) in attenuating the pressor response to laryngoscopy and intubation.

PATIENTS AND METHODS

This study was approved by the Human Investigation Committee of Kobe University School of Medicine and informed consent was obtained from all patients after a full explanation of the study. The present study consisted of two experimental plans, based on those used by Stoelting [4] and Mikawa and co-workers [8, 9].

Part 1 study

We studied 20 patients (ASA physical status I) to determine the time course and magnitude of arterial pressure (AP) and heart rate (HR) changes after a single rapid i.v. injection of ATP (Adethos, Kowa, Japan) during anaesthesia but in the absence of stimulation produced by intubation. Anaesthesia was induced with thiopentone 5 mg kg⁻¹ and the trachea was intubated after vecuronium 0.2 mg kg⁻¹. Anaesthesia was

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TABLE I. Patient data (mean (range or SEM)). No significant differences ($P > 0.05$)

	Part 1 study groups		Part 2 study groups		
	ATP 0.05 mg kg ⁻¹	ATP 0.1 mg kg ⁻¹	Control	ATP 0.05 mg kg ⁻¹	ATP 0.1 mg kg ⁻¹
No. patients	10	10	10	10	10
Sex (M:F)	3:7	4:6	4:6	3:7	3:7
Age (yr)	47.0 (31-63)	45.6 (27-60)	47.9 (32-65)	46.5 (30-59)	48.1 (31-64)
Weight (kg)	57.2 (3.3)	56.4 (3.0)	57.4 (3.5)	58.1 (3.7)	55.3 (3.9)

maintained with 1% enflurane and 50% nitrous oxide in oxygen for elective surgery and end-tidal carbon dioxide (PE'_{CO_2}) was measured by Datex Capnometer (Datex, Helsinki, Finland). Ventilation was controlled to maintain PE'_{CO_2} 4.2-4.9 kPa. Twenty patients were allocated randomly to groups A and B (table I). After AP and HR had stabilized, patients received ATP 0.05 mg kg⁻¹ (group A) or 0.1 mg kg⁻¹ (group B) as a single rapid i.v. injection. MAP was recorded continuously via a radial artery catheter. A unipolar electrocardiogram (ECG) lead II was displayed continuously on a cardiac monitor, and 15-s recordings were taken at each measurement period. All measurements were completed before surgical incision of the skin.

Part 2 study

We studied 30 normotensive patients (ASA physical status I) to determine the effect of prior administration of ATP on the cardiovascular responses to tracheal intubation. Stoelting reported that AP typically began to increase after about 15 s of laryngoscopy and became maximal after 30-45 s of direct laryngoscopy [10]. Furthermore, it has been documented that the maximum increase in MAP in response to 30 s of laryngoscopy followed by intubation was noted 15 s after intubation (45 s after starting laryngoscopy) [6] consistent with Stoelting's observations [10]. Based on the previously determined time course of MAP change following ATP, it was predicted that ATP administered simultaneously with the beginning of laryngoscopy would match the hypotensive effects of the drug with the onset and duration of increase in AP produced by laryngoscopy and tracheal intubation. No subject had received sedatives or anti-hypertensives. The patients were allocated randomly to three groups of 10: group C = saline (control group); group D = ATP 0.05 mg kg⁻¹ i.v.; group E = ATP 0.1 mg kg⁻¹ i.v. Premedi-

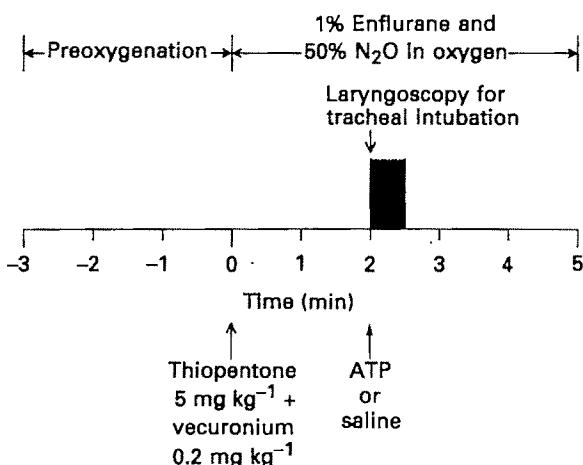


FIG. 1. Schematic diagram of the programme for the part 2 study to examine the effects of adenosine triphosphate (ATP) on cardiovascular changes after laryngoscopy and tracheal intubation. Shaded area denotes duration of laryngoscopy and intubation. ATP or saline was injected simultaneously with the start of laryngoscopy for tracheal intubation.

cation consisted of diazepam 0.1 mg kg⁻¹ by mouth 1 h and atropine 0.01 mg kg⁻¹ i.v. 30 min before induction of anaesthesia, respectively. The experimental programme is shown in figure 1.

On arrival of the patient in the operating room, a radial arterial catheter was inserted under local anaesthesia for continuous monitoring of MAP. HR was calculated from a 15-s portion of the ECG (lead II). After stabilization of AP and HR, while the patient breathed 100% oxygen via a mask for 3 min, anaesthesia was induced with thiopentone 5 mg kg⁻¹ followed by vecuronium 0.2 mg kg⁻¹ to facilitate tracheal intubation. Two minutes after administration of thiopentone and vecuronium, direct laryngoscopy was attempted, and tracheal intubation was completed within 30 s in all patients with the aid of a standard Macintosh laryngoscope blade. Either ATP 0.05 mg kg⁻¹, ATP 0.1 mg kg⁻¹ or saline (control) was injected

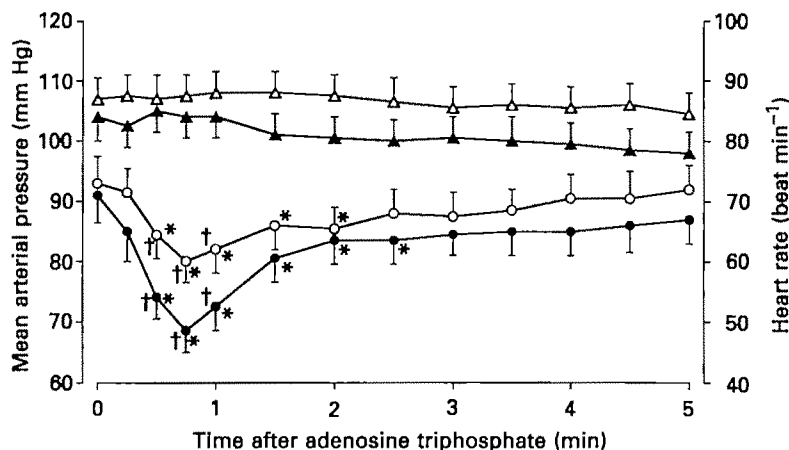


Fig. 2. Changes in mean arterial pressure (○, ●) and heart rate (△, ▲) (mean, SEM) after a single rapid i.v. injection of ATP 0.05 mg kg⁻¹ (○, △) and 0.1 mg kg⁻¹ (●, ▲) without concomitant laryngoscopy for intubation or surgery. $P < 0.05$: * *vs* basal value; † 0.05 mg kg⁻¹ *vs* 0.1 mg kg⁻¹.

rapidly via a peripheral i.v. cannula simultaneously at the start of direct laryngoscopy (2 min after thiopentone-vecuronium). All intubations were performed by one of the authors (K.M.) who was unaware of the nature of the injection. During anaesthesia, ventilation was assisted or controlled with 1% enflurane and 50% nitrous oxide in oxygen. PE_{CO_2} was maintained at 4.1–5.0 kPa, as measured using a Datex Capnometer by means of a catheter placed in the nostril until after the insertion of the tracheal tube, when sampling took place from T-piece connected to the tube. Serial HR and AP measurements were obtained immediately before induction and 1, 2, 2.5, 2.75, 3, 3.5, 4, 4.5 and 5 min after induction. The MAP, HR and the rate-pressure product (RPP) were compared with preinduction (basal) measurements within the same study groups and with corresponding measurements among the three groups (groups C–E).

Statistical analysis

Data were analysed by analysis of variance followed by Bonferroni's modification of *t* test. $P < 0.05$ was deemed significant.

RESULTS

Part 1 study

Figure 2 indicates the time course and magnitude of MAP and HR changes after a single i.v. administration of ATP 0.05 mg kg⁻¹ and 0.1 mg kg⁻¹ in patients anaesthetized with enflurane and nitrous oxide in oxygen in the absence of stimulation produced by laryngoscopy.

The magnitude of the decrease in MAP after ATP was influenced by the dose of ATP, while the onset of the decrease was not. MAP began to decrease 30 s after administration of ATP and was maximal after 45 s, with a return toward basal value apparent by 1.5 min and complete after 4 min (fig. 2.). HR did not differ significantly between the two doses.

Part 2 study

The five groups of the present study were comparable in age, weight and gender (table I). There was no significant difference among the three groups in MAP immediately before the start of laryngoscopy and at preinduction time (fig. 3). In response to laryngoscopy and intubation, MAP increased significantly in the control group, while the increase was significantly less in the ATP-treated groups. Administration of ATP 0.1 mg kg⁻¹ had a greater inhibitory effect on the increase in MAP associated with intubation than ATP 0.05 mg kg⁻¹. Although there was an increase in HR after induction and immediately after tracheal intubation in the three groups, there was no significant difference in HR among the three groups at any time (fig. 4). However, RPP was significantly smaller in ATP 0.05 or 0.1 mg kg⁻¹ treated groups compared with control after laryngoscopy and intubation. ATP 0.1 mg kg⁻¹ also had a greater inhibitory effect on the increase in RPP after intubation than did ATP 0.05 mg kg⁻¹.

No abnormalities in ECG were observed in any of the three groups. During this study, no patients were so hypotensive as to require pressor drugs.

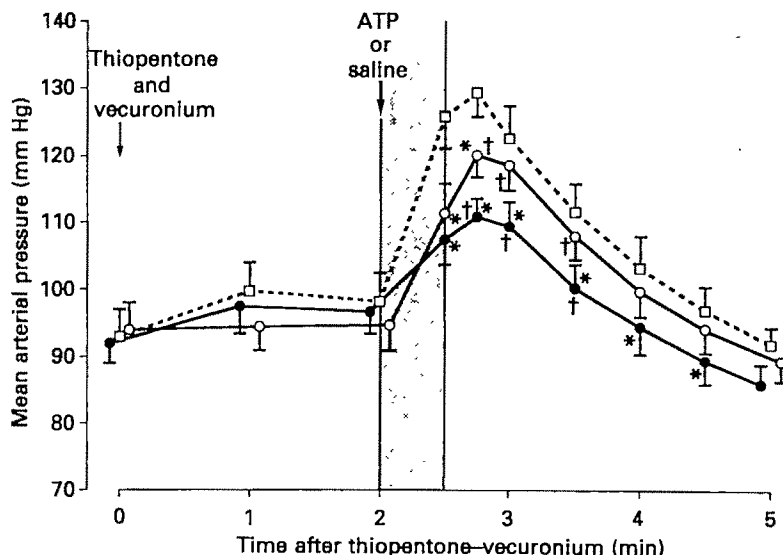


FIG. 3. Changes in mean arterial pressure (mean, SEM) after thiopentone-vecuronium and in response to laryngoscopy and tracheal intubation with prior ATP 0.05 mg kg^{-1} ($\circ$), 0.1 mg kg^{-1} ($\bullet$) or saline control ($\square$), administered i.v. simultaneously with the start of laryngoscopy. The stippled area denotes duration of laryngoscopy and tracheal intubation. $P < 0.05$: * vs control; † 0.05 mg kg^{-1} vs 0.1 mg kg^{-1} .

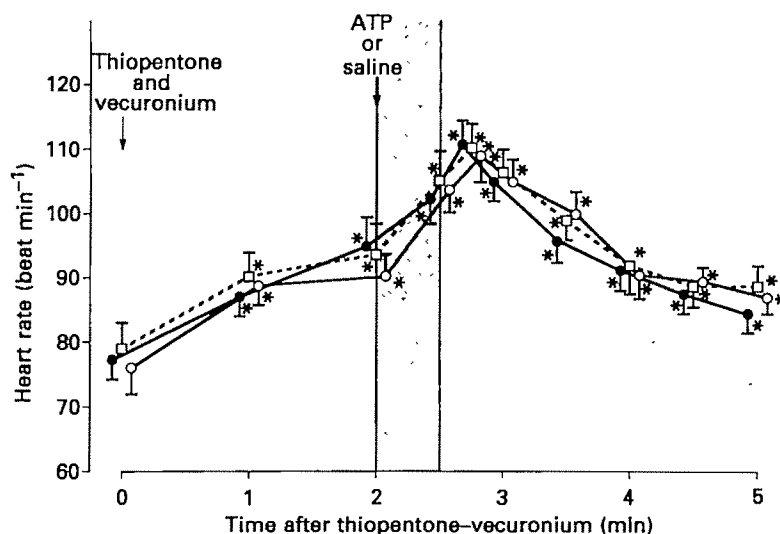


FIG. 4. Changes in heart rate (mean, SEM) after thiopentone-vecuronium and in response to laryngoscopy and tracheal intubation with prior ATP 0.05 mg kg^{-1} ($\circ$), 0.1 mg kg^{-1} ($\bullet$) or saline control ($\square$). The stippled area denotes duration of laryngoscopy and tracheal intubation. No difference among the three groups at any time; * $P < 0.05$ vs basal value within group.

DISCUSSION

This controlled, comparative and randomized study sought firstly to examine the time course and magnitude of AP and HR changes after administration of ATP during anaesthesia and, secondly, to assess its value in attenuation of the

pressor response to tracheal intubation. Since the report by Somlo in 1955 [11] ATP, which has negative chronotropic and dromotropic effects on the heart [12, 13], has been used for treatment of paroxysmal supraventricular tachycardia [14, 15]. In recent years there has been a growing interest in ATP, which is a potent vasodilator, as an agent

for controlled hypertension [16], and ATP has also been used for this purpose in patients [17, 18]. Although the precise mechanism of the vasodilator action of ATP is still unknown, it has been suggested that adenosine, to which parenterally administered ATP is degraded by phosphatases, mediates the vasodilator effect of ATP [19, 20].

This study has confirmed previous reports that intubation of the trachea following thiopentone and a neuromuscular blocking agent is associated with significant increases in HR and MAP. ATP in doses of 0.05 mg kg⁻¹ and 0.1 mg kg⁻¹ attenuated the increases in MAP and RPP after tracheal intubation compared with those of the control group, and the inhibitory effect was greater at doses of 0.1 mg kg⁻¹. As with other vasodilators which have been reported to exert no effect on the increase in HR associated with tracheal intubation, ATP failed to prevent tachycardia caused by laryngoscopy and intubation, despite the direct negative chronotropic effect of the agent. This negative chronotropic effect seems to have been masked by baroreceptor reflexes stimulated by hypotension. Because HR is a major determinant of myocardial oxygen supply and consumption, this effect may limit the usefulness of the drug.

The onset and duration of action of ATP were rapid and transient and there were no patients in the present study who had profound hypotension regardless of ATP doses, therefore it may be an appropriate drug to attenuate the hypertensive response to tracheal intubation.

ATP dilates coronary vessels, probably resulting in increased coronary blood flow (CBF) [21] and this may be an advantage in comparison with other drugs. In the second part of this study, reduction in diastolic AP was not so great in patients receiving ATP as to be a likely risk factor in myocardial ischaemia (55 mm Hg was the minimum diastolic AP in ATP-treated groups). RPP was attenuated after ATP. The maximum mean RPP after intubation in the ATP 0.1 mg kg⁻¹ group was 16767 mm Hg beat min⁻¹. Although this value is similar to an RPP of 17916 and 15868 mm Hg beat min⁻¹ in response to intubation in patients given hydralazine [22] and buprenorphine [23] before induction, respectively, it is still increased indicating that myocardial oxygen demand is high enough to be a risk factor in patients with coronary artery disease.

In conclusion, we have shown that a single rapid i.v. administration of ATP is a practical

method of attenuating the hypertensive response to tracheal intubation without an excessive decrease in diastolic AP. We recommend the use of ATP 0.1 mg kg⁻¹ as a supplement during induction for reducing the pressor response to intubation on the basis of RPP and MAP after intubation.

ACKNOWLEDGEMENT

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REFERENCES

1. Ng WS. Pathophysiological effects of tracheal intubation. In: Latta IP, Rosen M, eds. *Difficulties in Tracheal Intubation*. Eastbourne: Baillière Tindall, 1985; 12-35.
2. Miller FA, Dally FG. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. *British Journal of Anaesthesia* 1970; 42: 618-624.
3. Prys-Roberts C, Creene LT, Meloche R, Foëx P. Studies of anaesthesia in relation to hypertension, II: Haemodynamic consequences of induction and endotracheal intubation. *British Journal of Anaesthesia* 1971; 43: 531-547.
4. Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. *Anesthesia and Analgesia* 1979; 58: 116-119.
5. Fassoulaki A, Kaniaris P. Intranasal administration of nitroglycerin attenuates the pressor response to laryngoscopy and intubation of the trachea. *British Journal of Anaesthesia* 1983; 55: 49-52.
6. Hatano Y, Imai R, Komatsu K, Mori K. Intravenous administration of isosorbide dinitrate attenuates the pressor response to laryngoscopy and tracheal intubation. *Acta Anaesthesiologica Scandinavica* 1989; 33: 214-218.
7. Mikawa K, Ikegaki J, Maekawa N, Hoshina H, Tanaka O, Goto R, Obara H. Effects of prostaglandin E₁ on the cardiovascular response to tracheal intubation. *Journal of Clinical Anesthesia* 1990; 2: 420-424.
8. Mikawa K, Obara H, Kusunoki M. Effect of nicardipine on the cardiovascular response to tracheal intubation. *British Journal of Anaesthesia* 1990; 64: 240-242.
9. Mikawa K, Ikegaki J, Maekawa N, Goto R, Kaetsu H, Obara H. The effect of diltiazem on the cardiovascular response to tracheal intubation. *Anaesthesia* 1990; 45: 289-293.
10. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology* 1977; 47: 381-383.
11. Somlo E. Adenosine triphosphate in paroxysmal tachycardia. *Lancet* 1955; 268: 1125.
12. James TN. The chronotropic action of ATP and related compounds studied by direct perfusion of the sinus node. *Journal of Pharmacology and Experimental Therapeutics* 1965; 149: 233-247.
13. Belardinelli L, Mattos EC, Berne RM. Evidence for adenosine mediation of atrioventricular block in the

- ischemic canine myocardium. *Journal of Clinical Investigation* 1981; 68: 195-205.
14. Greco R, Musto B, Arienzo V, Alborino A, Garofalo S, Marsico F. Treatment of paroxysmal supraventricular tachycardia in infancy with digitalis, adenosine-5'-triphosphate, and verapamil: a comparative study. *Circulation* 1982; 66: 504-508.
 15. Belhassen B, Pelleg A, Shoshani D, Geva B, Laniado S. Electrophysiologic effects of adenosine-5'-triphosphate on atrioventricular re-entrant tachycardia. *Circulation* 1983; 68: 827-833.
 16. Fukunaga AF, Flacke WE, Bloor BC. Hypotensive effects of adenosine and adenosine triphosphate compared with sodium nitroprusside. *Anesthesia and Analgesia* 1982; 61: 273-278.
 17. Fukunaga AF, Ikeda K, Matsuda I. ATP-induced hypotensive anesthesia during surgery. *Anesthesiology* 1982; 57: A65.
 18. Fukunaga AF, Sodeyama O, Matsuzaki Y, Ikeda K, Matsuda I, Sato K. Hemodynamic and metabolic changes of ATP-induced hypotension during surgery. *Anesthesiology* 1983; 59: A12.
 19. Sollevi A, Lagerkranser M, Andreen M, Irestedt L. Relationship between arterial and venous adenosine levels and vasodilatation during ATP- and adenosine-infusion in dogs. *Acta Physiologica Scandinavica* 1984; 120: 171-176.
 20. Lagerkranser M, Irestedt L, Sollevi A, Andreen M. Central and splanchnic hemodynamics in the dog during controlled hypotension with adenosine. *Anesthesiology* 1984; 60: 547-552.
 21. Burnstock G. Purinergic receptors in the heart. *Circulation Research* 1980; 46: I175-I183.
 22. Davis MJ, Cronin KD, Cowie RW. The prevention of hypertension at intubation. A controlled study of intravenous hydralazine on patients undergoing intracranial surgery. *Anaesthesia* 1981; 36: 147-152.
 23. Khan FA, Kamal RS. Effect of buprenorphine on the cardiovascular response to tracheal intubation. *Anaesthesia* 1989; 44: 394-397.

EFFECTS OF PINDOLOL ON THE CARDIOVASCULAR RESPONSE TO TRACHEAL INTUBATION

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SUMMARY

Laryngoscopy and tracheal intubation often cause hypertension, tachycardia and arrhythmias, which may be exaggerated during rapid-sequence induction of anaesthesia. We have studied the efficacy of pindolol in attenuating the cardiovascular responses to laryngoscopy and intubation in patients receiving pindolol $2 \mu\text{g kg}^{-1}$ or $4 \mu\text{g kg}^{-1}$ 3 min before induction of anaesthesia in a double-blind design. The data were compared with those in a control group receiving saline. Each group consisted of 10 patients undergoing elective surgery. Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. and tracheal intubation was facilitated with vecuronium 0.2 mg kg^{-1} . Patients receiving saline showed a significant increase in mean arterial pressure and heart rate associated with tracheal intubation. These increases after tracheal intubation were reduced in pindolol $4 \mu\text{g kg}^{-1}$ treated patients compared with those in the control group ($P < 0.05$). Pindolol $2 \mu\text{g kg}^{-1}$ attenuated tachycardia in response to intubation but did not affect hypertension. These data suggest that a bolus injection of pindolol $4 \mu\text{g kg}^{-1}$ is a simple, practical and effective method for attenuating cardiovascular responses to laryngoscopy and tracheal intubation.

KEY WORDS

Arterial pressure: pindolol. Complications: hypertension. Intubation, tracheal: haemodynamic response.

Laryngoscopy and tracheal intubation often provoke a marked sympathetic response, resulting in hypertension and tachycardia [1-4]. Although transient, this response may be deleterious. In patients with coronary artery disease (CAD) or those with risk factors for CAD, myocardial ischaemia may occur during the induction-

intubation sequence [5]. Furthermore, such cardiovascular disturbances may be dangerous in patients suffering from cerebrovascular disease.

Many techniques and pharmacological agents have been described for control of hypertension or tachycardia associated with intubation [1, 6-9]. Among these, many authorities have advocated the use of β -adrenergic blocking agents, such as propranolol [10], esmolol [11], metoprolol [12] and labetalol [13]. The present study was designed to evaluate the efficacy of another β -adrenergic antagonist, pindolol, in attenuating the haemodynamic responses to laryngoscopy and intubation.

PATIENTS AND METHODS

This randomized, placebo-controlled and double-blind study was approved by the Human Investigation Committee of Kobe University School of Medicine and informed consent was obtained from all patients after a full explanation of the study.

The study group consisted of 30 normotensive patients (table I) (ASA physical status I) undergoing elective surgery. The patients were allocated randomly to three groups of 10: group A = saline i.v. (control group); group B = pindolol (Carvisken, Sandoz, Japan) $2 \mu\text{g kg}^{-1}$ i.v.; group C = pindolol $4 \mu\text{g kg}^{-1}$ i.v. Premedication consisted of diazepam 0.1 mg kg^{-1} by mouth 1 h and atropine 0.01 mg kg^{-1} i.m. 30 min before induction of anaesthesia. The experimental programme is shown in figure 1.

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TABLE I. Patient data (mean (range or SEM)). No significant differences ($P > 0.05$)

	Control (saline)	Pindolol $2 \mu\text{g kg}^{-1}$	Pindolol $4 \mu\text{g kg}^{-1}$
No. patients	10	10	10
Sex (M:F)	3:7	3:7	4:6
Age (yr)	43.4 (25–57)	44.7 (26–58)	45.1 (24–57)
Weight (kg)	57.6 (3.6)	59.5 (3.8)	56.7 (3.6)

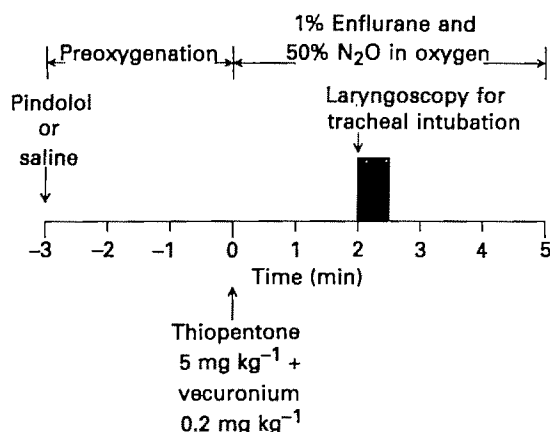


FIG. 1. Schematic diagram of the study to examine the effects of pindolol on cardiovascular changes following laryngoscopy and tracheal intubation. Shaded area denotes duration of laryngoscopy and intubation. Pindolol or saline was injected 5 min before the start of laryngoscopy for tracheal intubation.

Pindolol is a non-selective β -adrenergic antagonist exhibiting prominent intrinsic sympathomimetic activity (ISA). The ISA causes mild vasodilating properties, making this drug useful in the treatment of hypertension [14]. Compared with β -adrenergic antagonists devoid of ISA, such as propranolol and practolol, pindolol is less likely to cause myocardial depression, resting severe bradycardia, or a reduction in cardiac output. Thus pindolol is usually preferred for individuals with diminished cardiac reserve or a propensity for bradycardia [14]. The agent blocks exercise-induced increases in heart rate (HR) [14].

The rationale for administration of pindolol 5 min before the stimulus of laryngoscopy and intubation was based on data from a preliminary study and other laboratories. In our preliminary study, in which patients (ASA physical status I) were anaesthetized with 1% enflurane and 50% nitrous oxide in oxygen to determine the time courses and magnitudes of decreases in HR and

MAP after administration of various doses of pindolol in the absence of surgery, the effect of pindolol peaked 5–6 min after injection. Miyazaki and Fujita reported that the peak effect of i.v. pindolol on HR and AP changes and tachyarrhythmia, determined mainly in ASA I patients, occurred approximately 5 min after administration [15, 16]; their data are consistent with those of several studies mainly of ASA I patients that the anti-arrhythmic effect of this drug is apparent 1–7 min after injection [17, 18]. All investigators used pindolol $1\text{--}4 \mu\text{g kg}^{-1}$ in their studies [15–18]. Furthermore, the β -adrenergic blocking effect of pindolol is 5–20 times as potent as that of propranolol [1, 16]; because propranolol in a dose of $40 \mu\text{g kg}^{-1}$ has been confirmed to be useful in reducing haemodynamic changes after intubation [1], we used pindolol 2 and $4 \mu\text{g kg}^{-1}$ for this purpose. Thus it was predicted that the peak of action of pindolol 2 or $4 \mu\text{g kg}^{-1}$ administered 5 min before laryngoscopy would occur at the same time as the peak of hypertension and tachycardia produced by laryngoscopy and tracheal intubation.

In the operating room, a radial arterial catheter was inserted under local anaesthesia for continuous monitoring of MAP. HR was calculated from a 15-s portion of lead II of the ECG. After a 10-min stabilization period, the patients breathed 100% oxygen via a mask for 3 min. Subsequently, pindolol $2 \mu\text{g kg}^{-1}$ or $4 \mu\text{g kg}^{-1}$ or saline (control) was injected 5 min before starting direct laryngoscopy (3 min before administration of thiopentone–vecuronium). Immediately before administration of pindolol or placebo and induction of anaesthesia, AP and HR were recorded simultaneously by an independent observer. Anaesthesia was induced with thiopentone 5 mg kg^{-1} followed by vecuronium 0.2 mg kg^{-1} to facilitate tracheal intubation. Direct laryngoscopy was attempted 2 min after administration of thiopentone–vecuronium, and tracheal intubation was completed within 30 s in all patients, with the aid of a standard Macintosh laryngoscope blade. All intubations were performed by one of the authors (K. M.). The investigator and the patients were blinded to the identity of the experimental treatment. During anaesthesia, ventilation was assisted as required or controlled with 1% enflurane and 50% nitrous oxide in oxygen, and $P_{\text{E}'\text{CO}_2}$ was maintained at $4.2\text{--}4.9 \text{ kPa}$, measured with a Datex Capnometer by means of a catheter placed in the nostril until after the insertion of the

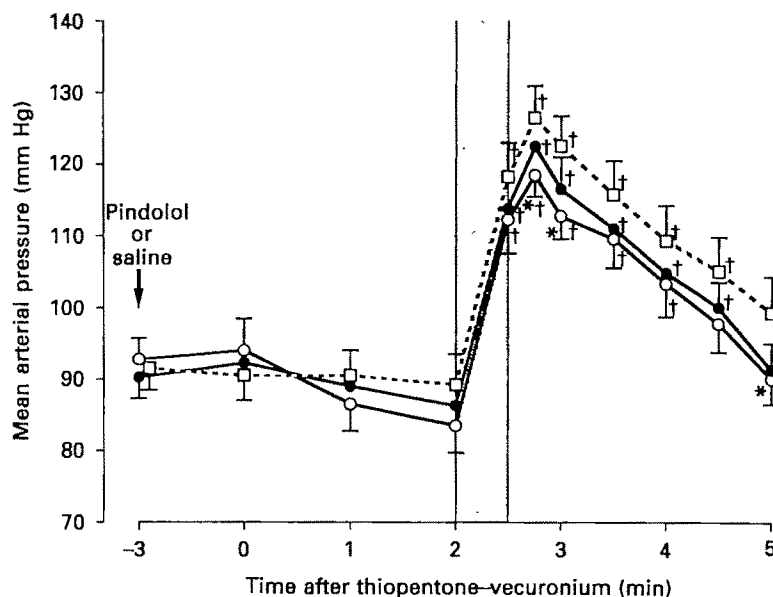


FIG. 2. Changes in mean arterial pressure (mean, SEM) after thiopentone-vecuronium and in response to laryngoscopy and tracheal intubation with pindolol $2 \mu\text{g kg}^{-1}$ (●), $4 \mu\text{g kg}^{-1}$ (○) or saline control (□), administered i.v 5 min before starting laryngoscopy. The stippled area indicates duration of laryngoscopy and tracheal intubation. $P < 0.05$: * vs control; † vs basal value (3 min before induction) within group.

tracheal tube, when sampling took place from a T-piece connected to the tube. Further measurements were taken 1, 2, 2.5, 2.75, 3, 3.5, 4, 4.5 and 5 min after administration of thiopentone-vecuronium by an independent observer. MAP, HR and rate-pressure product (RPP) were compared with corresponding measurements among the three groups (A-C) and with basal (3 min before induction) measurements within the same study group.

Statistical analysis was performed using analysis of variance followed by Bonferroni modification of t test. $P < 0.05$ was deemed significant.

RESULTS

The three groups were comparable in age, weight and gender (table I).

There were no significant differences among the three groups in MAP immediately before the start of the laryngoscopy and at preinduction time (fig. 2). In response to laryngoscopy and intubation, MAP increased significantly in the control group. The increases in MAP 15 s and 30 s after intubation were reduced in patients who received pindolol $4 \mu\text{g kg}^{-1}$ compared with those in the control group. However, administration of

pindolol $2 \mu\text{g kg}^{-1}$ failed to attenuate hypertension. There was no significant difference in HR among the three groups immediately before the start of laryngoscopy and preinduction (fig. 3). The HR increased significantly after intubation in the control group, while the increase was significantly less in the pindolol-treated groups (fig. 3). RPP was significantly smaller in pindolol 2 or $4 \mu\text{g kg}^{-1}$ groups compared with control after laryngoscopy and intubation. There was no difference in RPP between the two pindolol-treated groups at any time.

No abnormal changes in ECG were observed in any patient who received pindolol, although two patients in the control group had transient ventricular premature contractions. During this study, no patients had bradycardia severe enough ($\text{HR} < 50 \text{ beat min}^{-1}$) to require treatment and neither profound hypotension nor adverse respiratory effects were observed.

DISCUSSION

The present study has confirmed previous reports that tracheal intubation following thiopentone and a neuromuscular blocking agent causes significant increases in MAP, HR and RPP.

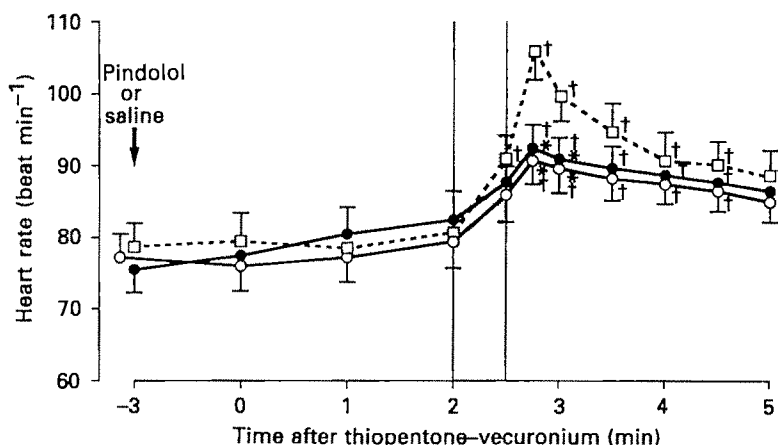


FIG. 3. Changes in heart rate (mean, SEM) after thiopentone-vecuronium and in response to laryngoscopy and tracheal intubation with pindolol $2 \mu\text{g kg}^{-1}$ (●), $4 \mu\text{g kg}^{-1}$ (○) or saline control (□). The stippled area denotes duration of laryngoscopy and tracheal intubation. $P < 0.05$: * vs control; † vs basal value (3 min before induction) within group.

Pindolol $4 \mu\text{g kg}^{-1}$ attenuated increases in these three variables after tracheal intubation compared with those of the control, whereas pindolol $2 \mu\text{g kg}^{-1}$ attenuated the increases in HR and RPP but not in MAP.

The use of i.v. β -adrenergic antagonists before induction of anaesthesia in patients not previously receiving these drugs is controversial [1]. In one report it was noted that practolol 12 mg, given to attenuate the pressor response to intubation, caused circulatory collapse and cardiac arrest in an 80-kg patient who was probably hypovolaemic [18]. In this situation, pindolol may be safer than other β -adrenergic blockers without ISA. Furthermore pindolol, which has been used in the management of angina pectoris [19], dilates renal arteries, resulting in increased renal blood flow [20] and this may be an advantage over other β -blockers which lack ISA.

RPP was attenuated after pindolol, mainly because of a decrease in the HR response. The maximum mean RPP after intubation in the pindolol $4 \mu\text{g kg}^{-1}$ group was $14263 \text{ mm Hg beat min}^{-1}$. This value compares favourably with the RPP of 15187 and $15868 \text{ mm Hg beat min}^{-1}$ in response to intubation in patients given prostaglandin E_1 [8] and buprenorphine [21] before induction, respectively.

In conclusion, we have shown that a single bolus i.v. administration of pindolol is a practical and effective method of attenuating hypertension and tachycardia in response to tracheal intubation.

On the basis of changes in MAP, HR and RPP, we recommend the use of a dose of pindolol $4 \mu\text{g kg}^{-1}$ as a supplement at the time of induction, for reducing the cardiovascular responses associated with intubation.

REFERENCES

1. Ng WS. Pathophysiological effects of tracheal intubation. In: Laro IP, Rosen M, eds. *Difficulties in Tracheal Intubation*. Eastbourne: Baillière Tindall, 1985; 12–35.
2. Miller FA, Dally FG. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. *British Journal of Anaesthesia* 1970; 42: 618–624.
3. Prys-Roberts C, Creene LT, Meloche R, Foëx P. Studies of anaesthesia in relation to hypertension. II: Haemodynamic consequences of induction and endotracheal intubation. *British Journal of Anaesthesia* 1971; 43: 531–547.
4. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology* 1977; 47: 381–384.
5. Estafanous FE, Tarazi RC. Systemic arterial hypertension associated with cardiac surgery. *American Journal of Cardiology* 1980; 46: 684–694.
6. Mikawa K, Obara H, Kusunoki M. The effect of nicardipine on the cardiovascular response to tracheal intubation. *British Journal of Anaesthesia* 1990; 64: 240–242.
7. Mikawa K, Ikegaki J, Maekawa N, Goto R, Kaetsu H, Obara H. The effect of diltiazem on the cardiovascular response to tracheal intubation. *Anaesthesia* 1990; 45: 289–293.
8. Mikawa K, Ikegaki J, Maekawa N, Hoshina H, Tanaka O, Goto R, Obara H. Effects of prostaglandin E_1 on the cardiovascular response to tracheal intubation. *Journal of Clinical Anesthesia* 1990; 2: 420–424.

9. Saitoh N, Mikawa K, Kitamura S, Maekawa N, Goto R, Yaku H, Yamada M, Obara H. Effects of trimethaphan on the cardiovascular response to tracheal intubation. *British Journal of Anaesthesia* 1991; 66: 340-344.
10. Safwat AM, Reitan JA, Misle GR, Hurley EJ. Use of propranolol to control rate-pressure product during cardiac anaesthesia. *Anesthesia and Analgesia* 1981; 60: 732-735.
11. Parnass SM, Rothenberg DM, Kerchberger JP, Ivankovich AD. A single bolus dose of esmolol in the prevention of intubation-induced tachycardia and hypertension in an ambulatory surgery unit. *Journal of Clinical Anesthesia* 1990; 2: 232-237.
12. Coleman AJ, Jordan C. Cardiovascular responses to tracheal intubation. Influence of beta-adrenoreceptor blockade with metoprolol. *Anaesthesia* 1980; 35: 972-978.
13. Leslie JB, Kalayjian RW, McLoughlin T, Plachetka JR. Attenuation of the hemodynamic responses to endotracheal intubation with preinduction intravenous labetalol. *Journal of Clinical Anesthesia* 1990; 1: 194-200.
14. Weiner N. Drugs that inhibit adrenergic nerves and block adrenergic receptors. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. New York: Macmillan, 1985; 181-214.
15. Miyazaki M, Fujita T. Study on various kinds of beta-adrenergic blockers in clinical anaesthesia. Part 3. LB-46 (pindolol). *Japanese Journal of Anaesthesia* 1971; 20: 589-597.
16. Miyazaki M, Fujita T. Clinical evaluation of various kinds of beta-adrenergic blockers in anaesthesia. *Japanese Journal of Anaesthesia* 1971; 21: 1-10.
17. Tosaki Y, Yoshiya I, Yoshikawa K, Onji Y. Anti-arrhythmic effect of LB-46 (a new anti-arrhythmic agent) during anaesthesia. *Japanese Journal of Anaesthesia* 1971; 20: 74-79.
18. Uchida M, Nozaki K, Komatsu T, Tomemori N, Yamazaki T. Anti-arrhythmic effects of a new beta-adrenergic blocking agent, LB-46, during general anaesthesia. *Hiroshima Journal of Anesthesia* 1972; 8: 99-105.
19. Mueller RA, Lundberg DBA. *Manual of Drug Interactions for Anesthesiology*. New York: Churchill Livingstone, 1988.
20. Farnon D, Curran J. Beta-receptor blockade and tracheal intubation. *Anaesthesia* 1981; 36: 803-805.
21. Rosenfeld J, Boner G, Wainer E. Renal function during acute and long term pindolol treatment in hypertensive patients with normal and decreased glomerular filtration. *British Journal of Clinical Pharmacology* 1982; 13: 237S-240S.

EFFECT OF CISAPRIDE ON MORPHINE ABSORPTION AFTER ORAL ADMINISTRATION OF SUSTAINED-RELEASE MORPHINE

D. J. ROWBOTHAM, K. MILLIGAN AND P. McHUGH

SUMMARY

We investigated the effect of cisapride 20 mg given orally with MST 20 mg on the absorption of morphine in a double-blind, placebo-controlled study. Cisapride increased significantly both plasma concentrations of morphine after 1 h and peak concentrations. There was no significant change in time to peak concentrations, sedation scores or percentage decrease in pupil diameters. Plasma concentrations of amylase were increased in three patients in the MST-placebo group and three in the MST-cisapride group. One patient in the MST-cisapride group developed acute pancreatitis.

KEY WORDS

Analgesics: oral morphine, plasma concentrations. Gastro-intestinal tract: cisapride. Pharmacokinetics: oral morphine.

MST Continus (Napp Laboratories) is a sustained-release tablet preparation releasing morphine over 12 h and is used most frequently for the treatment of pain associated with malignancy [1]. Cisapride is a new gastrointestinal prokinetic drug which increases the rate of gastric emptying, lower oesophageal sphincter pressure and small and large bowel motility [2]. Morphine delays gastric emptying and cisapride is more effective than metoclopramide in reversing this effect after i.m. administration [3].

Cisapride is now available generally and some patients may receive cisapride concomitantly with MST. Therefore, it was the purpose of this study to measure the effect of cisapride on morphine absorption after administration of MST.

PATIENTS AND METHODS

We studied 20 patients (aged 18-65 yr) undergoing minor general or orthopaedic surgery in the

afternoon. Local Ethics Committee approval and written informed patient consent were obtained. Patients were excluded if they were taking any concurrent medication, had any evidence of gastrointestinal disease or were scheduled for gastrointestinal surgery.

A light breakfast was taken at 06:30 on the day of surgery and the study commenced 2 h later. Patients were allocated randomly in a double-blind design to receive either MST 20 mg and placebo or MST 20 mg and cisapride 20 mg. Tablets were taken with water 50 ml and patients rested at 45° in bed for the duration of the study.

Blood 10 ml was taken from an indwelling venous cannula and visual analogue scores (VAS) for sedation were measured before and at 30-min intervals after drug administration. Plasma was separated immediately and stored at -20 °C before measurement of plasma morphine concentrations by HPLC using a technique described previously [4]. Pupil diameter was measured at 15-min intervals for 2 h and every 30 min thereafter using a pupillometer described by Asbury, Lear and Wortley [5].

The study was terminated after 5 h or when the patient left the ward for surgery.

Data were analysed using chi-square, Student's *t* and Mann-Whitney tests and MANOVA for repeated measures as appropriate.

RESULTS

There was a significant difference between groups in age, but not in weight, sex or type of surgery

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TABLE I. Patient data (mean (range or SD)). * $P < 0.05$ between groups

	Sex (M/F)	Age (yr)	Weight (kg)	Type of surgery
MST 20 mg + placebo ($n = 10$)	5/5	48.4 (34–62)	68.3 (10.1)	6 General 4 Orthopaedic
MST 20 mg + cisapride 20 mg ($n = 10$)	5/5	36.9 (18–58) *	67.8 (12.5)	7 General 3 Orthopaedic

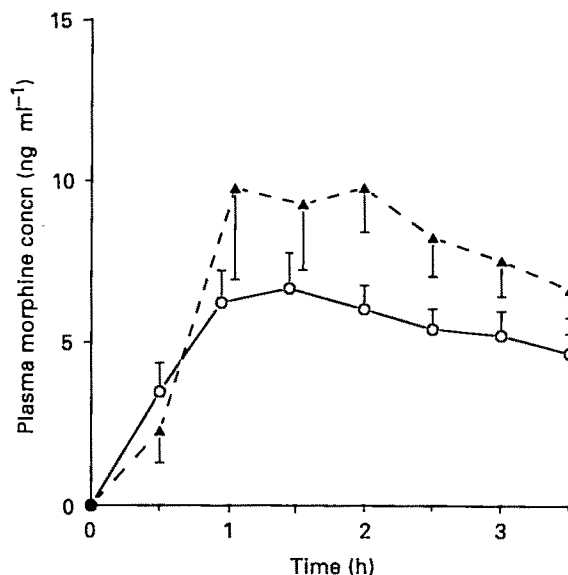


FIG. 1. Mean (SEM) plasma morphine concentrations after MST-placebo (○) or MST-cisapride (▲). Concentrations were significantly greater in the MST-cisapride group after 1 h ($P < 0.05$).

(table I). One patient was withdrawn from the study because of an adverse reaction (see below) and data from this patient were excluded from analysis. Complete data were available for only 3.5 h because of patients leaving the ward for surgery; these therefore, are the data presented.

Mean plasma concentrations of morphine were significantly greater in the MST-cisapride group after 1 h ($P < 0.05$) (fig. 1). Mean (SEM) maximum plasma concentration of morphine (C_{max}) was 8.8 (0.8) ng ml⁻¹ in the MST-placebo group and 13.7 (2.1) ng ml⁻¹ in the MST-cisapride group ($P < 0.05$). Median (range) time to maximum plasma concentration of morphine (t_{Cmax}) was 75 (30–150) min in the MST-placebo group and 90 (60–180) min in the MST-cisapride group (not significant).

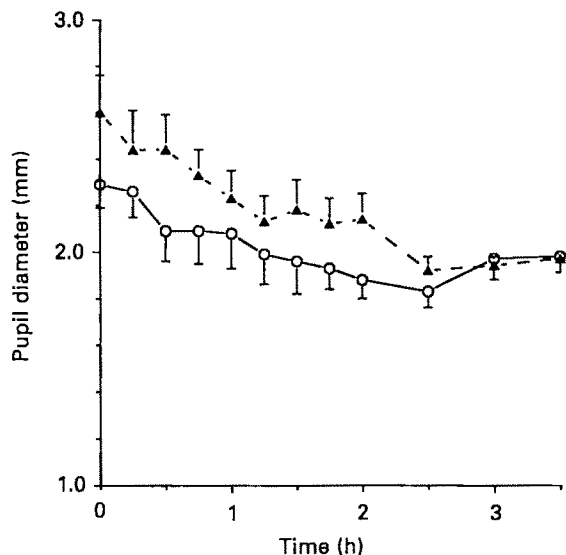


FIG. 2. Mean (SEM) pupil diameter (mm) after MST-placebo (○) or MST-cisapride (▲). Significant decrease within each group ($P < 0.05$ MST-placebo; $P < 0.01$ MST-cisapride). No significant difference between groups.

Mean pupil diameters at 3.5 h were significantly smaller in both groups compared with baseline values ($P < 0.05$ MST-placebo; $P < 0.01$ MST-cisapride) (fig. 2); mean (SEM) percentage decreases at this time were 12.4 (4.4)% and 22.1 (5.5)%, respectively. There was no significant difference between the groups in mean pupil diameters or percentage decrease at 3.5 h.

There was no significant difference in VAS sedation scores between the groups (fig. 3).

Adverse reactions

One patient in the MST-cisapride group was withdrawn from the study because of an adverse reaction. He was a healthy 50-yr-old male scheduled for haemorrhoidectomy, with no significant medical history or findings on examination. Preoperative white cell count and haemoglobin,

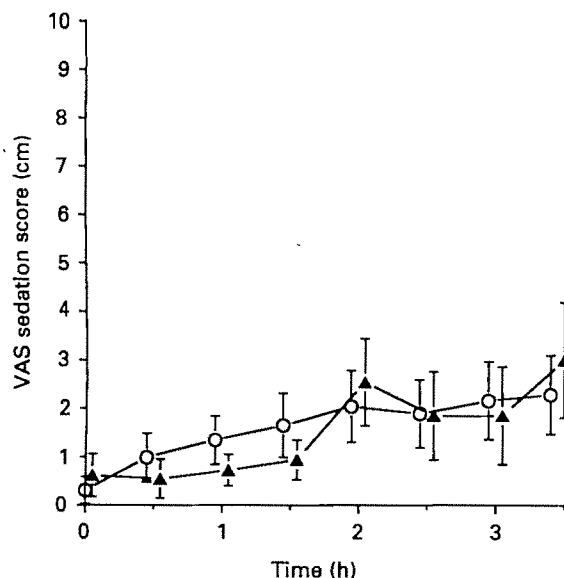


FIG. 3. Mean (SEM) VAS sedation score (cm) after MST-placebo (○) or MST-cisapride (▲). No significant differences.

and serum concentrations of electrolytes and urea were normal.

At 08:30 on the day of surgery, the patient was given cisapride 20 mg and MST 20 mg. Three hours later, he complained of epigastric discomfort and flatulence and, 30 min later, epigastric pain radiating to the back. At this stage he was withdrawn from the study and surgery cancelled. At 16:00 there were signs of upper abdominal guarding and a blood sample taken at this time revealed a plasma concentration of amylase 1251 u litre⁻¹ (normal range 10–82 u litre⁻¹; Enzyline Á-Amylase PNP 20, boiMérieux, France). A diagnosis of acute pancreatitis was made.

He was treated with i.v. fluids, nasogastric suction, analgesia, cefuroxime and metronidazole. No abnormality was detected on abdominal ultrasound. He made a full recovery with no complications and was discharged home 5 days later.

Subsequent analysis of the blood sample taken immediately before administration of the study medication revealed a normal plasma concentration of amylase (53 u litre⁻¹).

The reaction was reported to the Committee on Safety of Medicines and local Ethics Committee, Janssen Research Foundation and Napp Laboratories.

TABLE II. Increased plasma concentrations of amylase at 4 h (normal range 10–82 u litre⁻¹). Only patient No. 8 developed symptomatic pancreatitis

Patient No.	Group	Plasma amylase conc (u litre ⁻¹)	
		0 h	4 h
14	MST-placebo	46	134
15	MST-placebo	41	526
17	MST-placebo	98	1083
1	MST-cisapride	33	421
3	MST-cisapride	68	397
8	MST-cisapride	53	1251

At the end of the study, plasma concentrations of amylase were measured in plasma samples taken at 0 and 4 h in every patient (table II). Three patients in the MST-placebo group and three patients (including the one with pancreatitis) in the MST-cisapride group had increased concentrations of amylase at 4 h. No other patient complained of abdominal symptoms.

DISCUSSION

Cisapride increased plasma morphine C_{max} and concentrations after 1 h significantly when taken simultaneously with MST 20 mg in patients before surgery. Plasma morphine tC_{max} was unchanged. Pupil diameters decreased significantly in both groups after MST, but there was no significant difference between the groups. MST produced little preoperative sedation and there was no difference between the groups.

Plasma concentrations of morphine were similar to those found in other studies after MST [6–8]. Manara and others [7] investigated the effect of oral metoclopramide 10 mg on plasma concentrations of morphine and its effects after MST 20 mg. In contrast to cisapride in this study, metoclopramide had no effect on plasma morphine C_{max}. However, metoclopramide was associated with a change in median (range) plasma morphine tC_{max} values from 2.25 (0.5–5) h to 1.25 (0.5–2.5) h, respectively (*P* < 0.05). Corresponding values in this study were 1.25 (0.5–2.5) h and 1.5 (1–3) h. The findings of Manara and others are consistent with metoclopramide increasing the rate of absorption of morphine, presumably by enhancing gastric emptying.

The conclusions of the present study are less clear, as plasma tC_{max} was unaffected. Increased

plasma concentrations of morphine associated with cisapride may be caused by changes in volume of distribution, elimination rate constant, absorption rate and morphine release from the tablet. At present, there are no data to suggest that cisapride would affect any of these factors other than rate of absorption resulting from enhanced gastric emptying. However, this is speculative, as data from this study do not indicate which of these mechanisms is involved.

The effect of morphine on pupil diameter was demonstrated in both groups, but there was no significant difference between groups. Both groups in the present study showed little evidence of sedation. This is consistent with the findings of Kay and Healy [9] who demonstrated a mean preoperative 10-point VAS sedation score of 0.6 after MST 30 mg, compared with 0.3 after placebo. However, Manara and colleagues demonstrated higher sedation scores which were significantly greater during the first 90 min after MST 20 mg taken with metoclopramide. Differences in sedation may be caused by the earlier t_{Cmax} in the metoclopramide group or the possible analgesic effect of metoclopramide [10].

Cisapride increased plasma concentrations of morphine after administration of MST in this study, but no differences in pupil diameter or sedation were demonstrated, possibly because plasma concentrations of morphine were too small to show an effect. The effect of cisapride on the absorption of larger doses of morphine is not known but, if it is consistent with the findings of this study, then it may be associated with a significant increase in morphine effects.

One patient in the MST-cisapride group developed acute pancreatitis. Plasma concentrations of amylase, measured at the end of the study, were increased significantly in three (30%) patients in the MST-placebo group and three (30%) patients in the MST-cisapride group (including the patient who developed pancreatitis). Bogoch, Roth and Bockus [11] described a similar incidence of increased serum concentrations of amylase. I.m. morphine was administered to 39 medical patients with normal serum concentrations of amylase and blood samples were taken frequently over 24 h. Serum concentrations of amylase were increased in 11 (28%) patients. These findings were confirmed by Gould, Van Kley and Knight [12], who demonstrated increased serum concentrations of pancreatic amylase iso-enzyme in seven of 17 patients (41%)

after i.m. and s.c. morphine. No case of acute pancreatitis was reported by these authors, and we have been unable to find in the literature any reported case of acute pancreatitis after administration of morphine.

It is likely that increased plasma concentrations of amylase in this study were caused by morphine-induced spasm of the biliary tract and sphincter of Oddi—a side effect which has been recognized for some time [13]. However, cisapride was found also to increase contractions of the biliary tract and sphincter of Oddi in dogs, but decreased their resting tone [14]. No data are available as yet in man and no case of increased concentrations of amylase or pancreatitis has been reported with administration of cisapride alone. However, the number of patients exposed to cisapride is still relatively low.

ACKNOWLEDGEMENT

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REFERENCES

1. Twycross RG. The management of pain in cancer. In: Nimmo WS, Smith G, eds. *Anaesthesia*. Oxford: Blackwell Scientific Publications, 1989; 1216–1229.
2. Rowbotham DJ. Cisapride and anaesthesia. *British Journal of Anaesthesia* 1989; 62: 121–123.
3. Rowbotham DJ, Bamber PA, Nimmo WS. Comparison of the effect of cisapride and metoclopramide on morphine-induced delay in gastric emptying. *British Journal of Clinical Pharmacology* 1988; 26: 741–746.
4. Aitkenhead AR, Vater M, Achola K, Cooper CMS, Smith G. Pharmacokinetics of single dose i.v. morphine in normal volunteers and patients with end-stage renal failure. *British Journal of Anaesthesia* 1984; 56: 813–818.
5. Asbury AJ, Lear GA, Wortley D. Pupillometer for use during anaesthesia. *Anaesthesia* 1984; 39: 908–910.
6. Vater M, Smith G, Aherne GW, Aitkenhead AR. Pharmacokinetics and analgesic effects of slow-release morphine sulphate in volunteers. *British Journal of Anaesthesia* 1984; 56: 821–827.
7. Manara AR, Shelly MP, Quinn K, Park GR. The effect of metoclopramide on the absorption of oral controlled release morphine. *British Journal of Clinical Pharmacology* 1988; 25: 518–521.
8. Lew JKL, Mobley KA, Achola KJ, Horne M, Smith G. Postoperative absorption of controlled release morphine sulphate. *Anaesthesia* 1989; 44: 101–103.
9. Kay B, Healy TEJ. Premedication by controlled-release morphine. *Anaesthesia* 1984; 39: 587–589.
10. Ramaswamy S, Bapna JS. Analgesic effect of metoclopramide and its mechanism. *Life Sciences* 1986; 38: 1289–1292.
11. Bogoch A, Roth JLA, Bockus HL. The effects of

- morphine on serum amylase and lipase. *Gastroenterology* 1954; 26: 697-708.
12. Gould RJ, Van Kley H, Knight WA. Elevation of serum amylase levels after narcotic administration. *Southern Medical Journal* 1982; 75: 711-712.
13. Jaffe JH, Martin WR. Narcotic analgesics and antagonists. In: Goodman LS, Gilman A, eds. *The Pharmacological Basis of Therapeutics*, New York: MacMillan Publishing Co., 1975; 254.
14. Nakayama S, Neya T, Yamasato T, Takaki M, Itano N. Effects of cisapride on the motility of digestive tract in dogs and guinea pigs. *Japanese Journal of Smooth Muscle Research* 1985; 21: 1-9.

GASTRIC EMPTYING AND SMALL BOWEL TRANSIT IN MALE VOLUNTEERS AFTER I.M. KETOROLAC AND MORPHINE

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SUMMARY

Ten male volunteers were studied in a randomized, double-blind crossover trial. Each received ketorolac tromethamine 30 mg and morphine sulphate 10 mg i.m. at an interval of 2 weeks. After a standard radiolabelled meal, gastric emptying half-time (GE) and small intestinal transit time (SIT) were measured using a gamma camera. Small intestinal transit time was measured also from end-tidal breath hydrogen (ETH), and overall gastrointestinal motility by time to first flatus (TFF). Mean GE, SIT and TFF were significantly prolonged by morphine compared with ketorolac ($P < 0.03$); ETH was prolonged also, but the difference was not significant. There were no significant correlations between SIT, ETH and TFF. Most subjects reported adverse effects after morphine, but only one after ketorolac.

KEY WORDS

Analgesics: ketorolac, morphine. Gastrointestinal system: gastric emptying.

Opioids have been used for a considerable time for relief of postoperative pain. However, these drugs delay gastric emptying and intestinal motility [1-3]; this, in turn, contributes to nausea and vomiting and is also unhelpful if patients require fluids, nutrition or medication enterally. In addition, the gastrointestinal tract may be affected adversely by the anaesthetic agent, and so a powerful analgesic which does not prolong gastrointestinal transit time should be advantageous.

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug which is being evaluated for the relief of moderate to severe pain, especially in

the immediate postoperative period [4]. In this study, the effects of ketorolac on gastric emptying and small intestinal transit were compared with those of morphine.

SUBJECTS AND METHODS

Investigations were performed in normal volunteers using a technique similar to that described previously [5] and doses of ketorolac (30 mg) and morphine (10 mg) which were demonstrated to be equally effective in relieving pain after cholecystectomy when administered i.m. [4]. The study was not complicated by the use of other drugs [6]. Ten normal, healthy males were recruited (mean (SD) age, height and weight 32.5 (4.5) yr, 1.73 (0.09) m and 80.4 (15.4) kg, respectively). Each subject gave written, informed consent and the study was approved by the hospital Ethics Committee. It also conformed with the Declaration of Helsinki and the Association of the British Pharmaceutical Industry guidelines for medical experiments in non-patient human volunteers. Subjects who had asthma, previous bowel surgery or gut disease, a known allergy or previous adverse reaction to salicylate or non-steroidal anti-inflammatory drugs, or a known intolerance to morphine were excluded, as were subjects who

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smoked [7]. One week before the first assessment, each subject was given a medical examination and a blood sample was taken for measurement of haemoglobin, red and white blood cell counts, platelets, urea, creatinine, bilirubin, serum glutamic oxaloacetic transaminase, alkaline phosphatase, total proteins, albumin and gamma glutamyl transferase. These investigations were repeated at the end of the study and it was confirmed that no abnormalities had been detected in any of the volunteers on either occasion.

A double-blind crossover design was adopted and the medications were allocated according to a predetermined randomization schedule. Five subjects received a single dose of ketorolac 30 mg for the first assessment and a dose of morphine 10 mg for the second; the order of the drugs was reversed for the remaining five volunteers and an interval of 2 weeks was allowed between each assessment. The drugs were administered by i.m. injection into the vastus lateralis. Any adverse effects were recorded and the volunteers were followed up for 1 week after completion of the measurements.

Each subject fasted overnight for 12 h; 30 min after administration of the injection, a standard meal with water 50 ml was eaten within 10 min. The meal consisted of baked beans 120 g and scrambled eggs 90 g without additional fat. Human serum albumin macroaggregates (TCK 8 from CIS Ltd) labelled with technetium-99m 8 MBq were incorporated into the eggs during cooking. This radiopharmaceutical is not absorbed by the gut and so it may be used to demonstrate the gastrointestinal tract by imaging with a gamma camera. Baked beans contain the indigestible oligosaccharides, stachyose and raffinose, which serve as a substrate for hydrogen production in the large intestine. No further eating or drinking was allowed until the conclusion of the test. Subsequent measurements of gastric emptying and intestinal transit were made with reference to the time at which the meal was finished.

Gastric emptying rate was measured by recording data from a gamma camera (IGE 400 AT with a low energy, general purpose, parallel hole collimator) positioned over the stomach region. This camera was interfaced to an Elscint Apex 009 data processor and a series of 60-s images was acquired using a 256 × 256 pixel matrix. Pairs of anterior and posterior views were taken at 10-min intervals for 90 min, at 30-min intervals for the next 90 min and then hourly for up to 7 h. All

images were acquired with the volunteer in the supine position, but seated on a chair between scans. An activity-time curve was generated by totalling the counts within a stomach region of interest, calculating the geometric mean for each pair of opposed views, applying an appropriate correction for radioactive decay and expressing each value as a percentage of that obtained at 10 min. The relative activity at the reference time (zero) was extrapolated from a single exponential fitted to the early data. Subsequently, the gastric emptying half-time (GE), the time at which 50 % of the original activity had left the stomach, was interpolated from the activity-time curve. In those cases where GE was longer than the study period, it was estimated by extrapolation of a single exponential fitted to the later part of this curve [8]. The time at which 90 % of the original activity had left the stomach (T90) was estimated in the same way.

Small intestinal transit time was measured by two different methods. First, the time for radioactivity to appear over the caecum (SIT) was assessed using the above gamma camera data and additional anterior views such that the overall intervals between images were as follows: 10 min for the first 150 min, 20 min for the next 150 min and 1 h subsequently. The caecum was identified with the aid of a small radioactive marker source positioned 2 cm medial to the anterior superior iliac spine [5]. Second, samples of exhaled air were collected for analysis of hydrogen concentration, at 10-min intervals for 2 h and subsequently every 20 min. End-tidal samples were obtained after prolonged expiration by aspiration into a 20-ml plastic syringe from the side arm of a modified Haldane-Priestley tube [9]. Hydrogen concentration was measured immediately with a hydrogen monitor (GMI Medical Ltd) [10] which had been calibrated with a GMI standard calibration gas mixture (SGP R01A) containing hydrogen 96 p.p.m. in air. These data were plotted and the time at which end-tidal breath hydrogen increased (ETH) was noted by visual inspection of the curves.

In addition, time to first flatus (TFF) was recorded by attaching an open manometer catheter (Lecro-cath) to the inside of the subject's thigh, close to the anus. This was connected to a Datex Normocap infra-red carbon dioxide analyser which was linked to a graph recorder (Curken 125-1). TFF was recorded as the time at which the concentration of carbon dioxide in-

creased to 0.5% or more [11]. The volunteers were also asked to note when they passed flatus.

Results were analysed by Student's paired *t* test and linear regression; differences and correlations were taken as significant when $P < 0.05$.

RESULTS

There were no adverse effects after ketorolac apart from one volunteer who complained of paraesthesiae over the face and tongue and both upper and lower limbs. In contrast, nine of the subjects reported immediate side effects after administration of morphine: six complained of belching, two of nausea and vomiting, five of somnolence, one of itching, one of oesophageal reflux, one of paraesthesiae over both hands and five of pain at the sites of injection. In addition, one volunteer developed headache, lumbo-sacral backache and increased urinary frequency 1 week after the investigations (this subject had also received morphine 2 weeks previously for measurements that had to be abandoned because of equipment problems). Serum urea, electrolytes and creatinine concentrations and urine analysis were normal, as were a full blood count and liver function tests. Symptoms resolved spontaneously after 1 week.

GE, SIT, TFF and T90 were prolonged significantly after morphine compared with ketorolac ($P < 0.03$); ETH was also greater but in this instance the difference was not significant (table

TABLE I. Summary of the results for gastric emptying and small intestinal transit time in 10 male volunteers after i.m. ketorolac and morphine (mean (SD)). GE = gastric emptying half-time; T90 = time at which 90% of the meal had left the stomach; SIT = time for radioactivity to appear over the caecum; ETH = time of increase in end-tidal breath hydrogen concentration; TFF = time to first flatus

	Time (min)		P (paired <i>t</i> test)
	Ketorolac	Morphine	
GE	62 (17)	214 (140)	< 0.02
T90	134 (18)	612 (489)	< 0.02
SIT	119 (94)	232 (99)	< 0.03
ETH	201 (85)	254 (103)	ns
TFF	120 (84)	288 (163)	< 0.02

I). In general, the range of values also was much greater with the former drug and gastrointestinal symptoms were associated with prolongation of gastric emptying. With morphine, GE was longer than the duration of the study (420 min) in two subjects and was estimated by extrapolation using an exponential fit; the same was true for T90 in six of the volunteers. In one subject, there was no obvious increase in breath hydrogen during the morphine study and so ETH was recorded as greater than 420 min. With the same drug, carbon dioxide concentration did not reach 0.5% in four volunteers and so TFF was recorded similarly. Such problems were not found with ketorolac.

Figure 1 shows mean gastric emptying curves; in figure 2, the cumulative frequency of results in

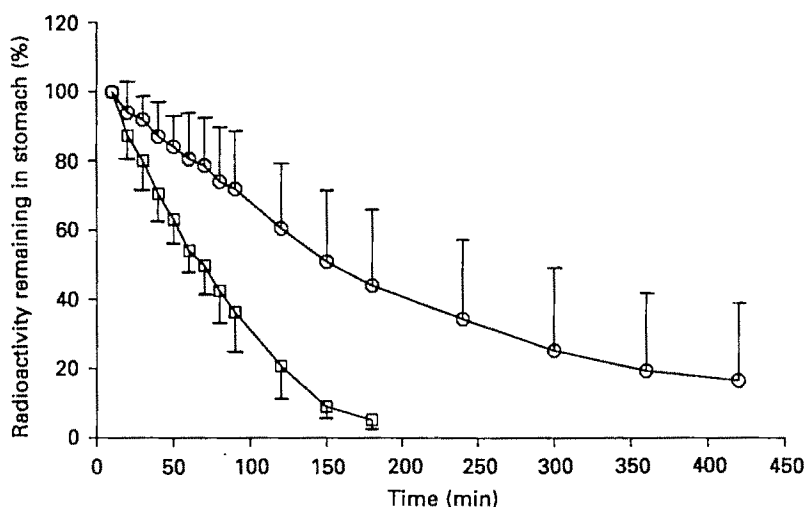


FIG. 1. Mean (SEM) gastric emptying curves for 10 male volunteers following the administration of ketorolac (□) and morphine (○).

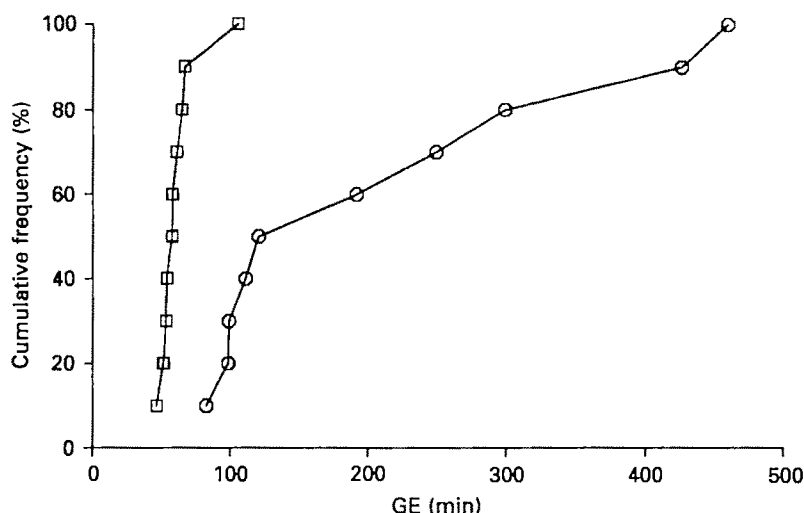


FIG. 2. Cumulative frequency of results in gastric emptying against half-time (GE) in 10 normal male volunteers after receiving ketorolac (□) and morphine (○).

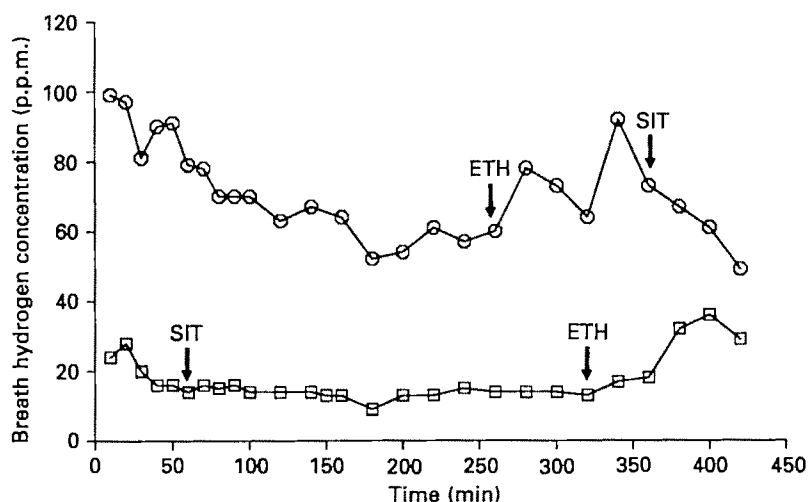


FIG. 3. Variation in end-tidal breath hydrogen concentration after the administration of ketorolac (□) and morphine (○). The estimated times at which the concentration began to increase (ETH) are shown, together with the small intestinal transit time (SIT) measured by the appearance of radioactivity in the caecum on the gamma camera images. (The initial increase in the hydrogen concentration is attributable to the gastro-ileal effect.)

gastric emptying are plotted against half-time [5]. Values of GE were ranked separately in increasing order for the two drugs; as there were 10 volunteers, each individual datum contributes 10% to the cumulative frequency. After ketorolac, GE was shorter than 70 min in nine of the subjects, while it was longer than 80 min for all volunteers after morphine (fig. 2). Its greatest

value with ketorolac was 105 min and in this individual there was little difference with both drugs, although T90 was considerably shorter with ketorolac (156 min) compared with morphine (254 min). In one other individual, both the rate and pattern of gastric emptying were similar for the two drugs. This latter case was the only instance in which SIT was greater after ketorolac

(360 min) compared with morphine (150 min). With the former drug, SIT was shorter than 100 min in seven of the subjects, whereas it was always greater than this after morphine.

In all but three cases, ETH was greater after morphine. The difficulties associated with precise estimation of ETH are illustrated in figure 3, which shows the variation in end-tidal breath hydrogen concentration in the same individual after the administration of ketorolac and morphine. Whereas the time at which breath hydrogen concentration began to increase is relatively easily estimated for the former, it is not so for the latter. (The initial increase in hydrogen concentration after the test meal is a normal phenomenon as a result of the passage into the caecum of a meal eaten the night before—the gastro-ileal effect.) In this particular example, the estimated value of ETH was greater after ketorolac than after morphine, and even when the estimation of ETH was relatively easy, SIT as assessed from the gamma camera images was considerably shorter.

After ketorolac, the maximum value of TFF was 252 min, while morphine produced values in excess of 380 min in six subjects. Some difficulties were experienced with this measurement also. A carbon dioxide concentration of 0.5% or greater was noted in 16 of the 20 investigations, but in four of these the volunteer did not admit to passing flatus. On occasions, small increases of 0.1–0.3% (but sometimes up to 0.5%) were recorded as the subject ascended or descended the imaging table. Such readings were regarded as artefacts produced by the expression of flatus during movement and a value of TFF was noted only when 0.5% was exceeded with the subject seated during an interval between gamma camera measurements.

There were no significant correlations among GE, SIT, ETH and TFF after administration of either morphine or ketorolac. Furthermore, the values of each variable after one drug did not correlate significantly with its values after the other.

DISCUSSION

The results of the imaging investigations indicate significant prolongation of both the gastric emptying half-time (GE) and small intestinal transit time (SIT) by i.m. administration of morphine 10 mg compared with ketorolac 30 mg. There was also almost complete absence of other adverse effects associated with the use of ketorolac. As

most routine postoperative analgesics are given i.m., the absence of pain at the site of injection should make ketorolac particularly attractive to patients.

In a previous study [5], similar techniques were used to measure the effects of a saline placebo and morphine 5 mg but, in this case, the drugs were administered by i.v. injection. However, it has been shown that absorption of ketorolac after i.m. injection is rapid and its bioavailability complete compared with i.v. administration [12], and so the similar mean values of GE and SIT obtained with ketorolac (62 and 119 min, respectively) and placebo (69 and 145 min, respectively [5]) suggest that the former does not depress the motility of the gastrointestinal tract. Morphine is also absorbed rapidly and its bioavailability is complete after i.m. injection [13]. The results of the two studies suggest that doubling the dose of morphine from 5 mg to 10 mg increased both mean GE (from 84 to 214 min) and mean SIT (from 186 to 232 min). Even morphine 5 mg significantly prolongs SIT compared with placebo [5], and so the advantage of ketorolac as a powerful analgesic without any effect on gut motility might be lost if an opioid were administered concomitantly. Hence it would be valuable to use ketorolac by itself (in day surgery, for example) rather than for its morphine sparing properties [14] if gastrointestinal depression is to be avoided.

The mean time for 90% of the radioactive meal to leave the stomach (T90) was significantly greater for morphine (10.2 h) compared with ketorolac (2.2 h); with the latter drug, the maximum value was 2.8 h. In contrast, after morphine, T90 exceeded 7 h in 60% of the subjects and its greatest value was 25.4 h, although this was obtained by extrapolation using an exponential fit. This suggests that the common practice of starving a patient for 6 h before anaesthesia is adequate if an analgesic which does not depress gastrointestinal motility has also been used. However, this is not the case if morphine 10 mg or more has been administered before or shortly after the last meal.

As a method of measuring small intestinal transit time, a gamma camera is both relatively expensive and inaccessible (because of the demands of routine clinical investigations). End-tidal breath hydrogen excretion has been proposed as a simpler method [8, 15]. However, in contrast with the results of a previous investigation [5], in this study no significant correlation was found

between SIT and ETH. It is likely that this reflected the imprecision associated with both these measurements, especially that of ETH. On average, ETH was longer than SIT after administration of both drugs, and so it may be that the gamma camera is able to detect a small quantity of the radioactive meal in the caecum, whereas a larger mass is required for production of a measurable amount of hydrogen by bacterial growth in the large intestine. Furthermore, if ketorolac really does not depress gastrointestinal motility, the fact that SIT was deemed to be longer with ketorolac than with morphine in only one individual (compared with three for ETH) suggests the superiority of the gamma camera technique.

Time to first flatus is a measure of co-ordinated bowel function [11]. After administration of morphine, the average value of TFF was greater than both measures of small intestinal transit (SIT and ETH), but the same was not true after ketorolac. In only two subjects was TFF longer after ketorolac compared with morphine and, unlike ETH, the mean values were significantly different for the two drugs. However, this was caused partly by the fact that, after morphine, in four subjects an increase of carbon dioxide concentration to 0.5% was not recorded over the 7-h study period and TFF was set at this value. This may reflect a genuine delay in flatus production or instrumental insensitivity, and so it is unclear if a measurement of TFF offers any advantage over end-tidal breath hydrogen concentration.

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REFERENCES

1. Nimmo WS, Wilson J, Prescott LF. Narcotic analgesics and delayed gastric emptying during labour. *Lancet* 1975; 1: 890-893.
2. Todd JG, Nimmo WS. Effect of premedication on drug absorption and gastric emptying. *British Journal of Anaesthesia* 1983; 55: 1189-1193.
3. Nimmo WS, Heading RC, Wilson J, Prescott LF. Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone. *British Medical Journal* 1979; 2: 1189.
4. Power I, Douglas E, Noble DW, Spence AA. Comparison of i.m. ketorolac tromethamine and morphine sulphate for pain relief after cholecystectomy. *British Journal of Anaesthesia* 1990; 64: 395P-396P.
5. Yukioka H, Rosen M, Evans KT, Leach KG, Hayward MWJ, Saggi GS. Gastric emptying and small bowel transit times in volunteers after intravenous morphine and nalbuphine. *Anaesthesia* 1987; 42: 704-710.
6. Heading RC, Nimmo J, Prescott LF, Tothill P. The dependence of paracetamol absorption on the rate of gastric emptying. *British Journal of Pharmacology* 1973; 47: 415-421.
7. Tadesse K, Eastwood M. Breath hydrogen test and smoking. *Lancet* 1977; 2: 91.
8. Read NW, Miles CA, Fisher D, Holgate AM, Kime ND, Mitchell MA, Reeve AM, Roche TB, Walker M. Transit of a meal through the stomach, small intestine and colon in normal subjects and its role in the pathogenesis of diarrhoea. *Gastroenterology* 1980; 79: 1276-1282.
9. Metz G, Gassull MA, Leeds AR, Blendis LM, Jenkins DJA. A simple method of measuring breath hydrogen in carbohydrate malabsorption by end-expiratory sampling. *Clinical Science and Molecular Medicine* 1976; 50: 237-240.
10. Bartlett K, Dobson JV, Eastham E. A new method for the detection of hydrogen in the breath and its application to acquired and inborn sugar malabsorption. *Clinica Chimica Acta* 1980; 108: 189-194.
11. Yukioka H, Bogod DG, Rosen M. Recovery of bowel motility after surgery. *British Journal of Anaesthesia* 1987; 59: 581-584.
12. Jung D, Mroszczak E, Bynum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. *European Journal of Clinical Pharmacology* 1988; 35: 423-425.
13. Stanski DR, Greenblatt DJ, Lowenstein E. Kinetics of intravenous and intramuscular morphine. *Clinical Pharmacology and Therapeutics* 1978; 24: 52-59.
14. Gillies GWA, Kenny GNC, Bullingham RES, McArdle CS. The morphine sparing effect of ketorolac tromethamine. *Anaesthesia* 1987; 42: 727-731.
15. Bond JH jr, Levitt MD. Investigation of small bowel transit time in man utilising pulmonary hydrogen (H_2) measurements. *Journal of Laboratory and Clinical Medicine* 1975; 85: 546-555.

PRELIMINARY STUDY TO ASSAY PLASMA AMETHOCAINE CONCENTRATIONS AFTER TOPICAL APPLICATION OF A NEW LOCAL ANAESTHETIC CREAM CONTAINING AMETHOCAINE

B. MAZUMDAR, A. A. TOMLINSON AND G. C. FAULDER

SUMMARY

Plasma concentrations of amethocaine were measured after topical application of amethocaine cream 2 g (5% w/w) to the dorsum of the right hand of 10 adult volunteers. The cream was applied for 240 min and plasma was assayed for amethocaine and its metabolite p-n-butylaminobenzoic acid at 0, 30, 60, 90, 120 and 240 min in all 10 volunteers, and at 360 min in seven volunteers, by high pressure liquid chromatography. No amethocaine was detected in the plasma of seven volunteers. Plasma concentrations of amethocaine up to 0.20 mg litre⁻¹ were observed in three volunteers. No significant side effects were seen and pain scores on insertion of a 16-gauge cannula were 0 in all subjects. We conclude that the absence of clinical toxicity in the 10 healthy volunteers was a reflection of slow absorption and tissue hydrolysis of amethocaine after topical dermal application.

KEY WORDS

Anaesthetics, local: topical amethocaine, plasma concentration.

The use of local anaesthetic cream to provide topical anaesthesia for venepuncture has increased in recent years with the advent of a eutectic mixture of lignocaine and prilocaine (EMLA). Since the introduction of this cream into clinical practice, other local anaesthetic agents have been re-evaluated for topical use, and it has been suggested that amethocaine possesses the best topical anaesthetic properties [1]. A study comparing a local anaesthetic cream containing amethocaine with EMLA, found that the

amethocaine cream had a more rapid onset of action, had a longer duration of action and provided equally effective analgesia as EMLA [2]. An editorial accompanying that paper considered the amethocaine cream promising, but expressed concern about its toxicity [3]. The aim of the present study was to address this concern by monitoring healthy volunteers for clinical evidence of toxicity, following the prolonged application of topical amethocaine cream. In addition, serial blood samples were taken for assay of plasma concentrations of amethocaine and its metabolite p-n-butylaminobenzoic acid (BBA), to correlate evidence of clinical toxicity, if present, with plasma concentrations of the drug and metabolite.

SUBJECTS AND METHODS

After Ethics Committee approval we studied 10 healthy adult volunteers who gave informed consent. Allergy to creams and local anaesthetics, or known pseudocholinesterase deficiency, were the only exclusion criteria. Full resuscitation facilities were available during the study.

Baseline heart rate and arterial pressure were recorded using ECG and automatic arterial pressure monitoring (Dinamap). The ECG was monitored continuously throughout the study, and arterial pressure was recorded at 5-min

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intervals for the first 15 min, at 15-min intervals for the next 45 min and at 30-min intervals for the remaining 180 min. A 20-gauge cannula was inserted into a left forearm vein without local anaesthesia and retained for the period of the study for venous blood sampling.

At time 0, amethocaine cream 2 g (5% amethocaine w/w in methylcellulose) was applied to a 6-cm² area of skin on the dorsum of the right hand and covered with a clear occlusive dressing. After 4 h the cream was removed, and analgesia assessed by insertion of a 16-gauge cannula into a vein at the anaesthetized site. The subjects scored pain as 0 = no pain; 1 = minimal pain; 2 = moderate pain; 3 = severe pain. Any side effects reported by the subjects were recorded.

Ten-millilitre aliquots of venous blood were obtained at times 0, 30, 60, 120 and 240 min in all 10 subjects, and in seven subjects at 360 min. The blood was collected in heparinized glass bottles containing 10% sodium metabisulphite 0.2 ml and 2-molar sodium hydroxide 0.2 ml, to prevent enzymatic hydrolysis of amethocaine, as recommended by Yang and colleagues [4]. Plasma was separated by immediate centrifugation and stored at -70 °C until required for analysis.

The plasma was assayed for amethocaine and its metabolite BBA by high pressure liquid chromatography (HPLC) using a method based on that described by Yang and colleagues [4], and Menon and Norris [5]. The internal standards for amethocaine and BBA were salicylic acid and propiophenone, respectively. The mobile phase was prepared from water, acetonitrile and methanol (3:1:1 v/v) containing sulphuric acid 600 µl litre⁻¹, sodium sulphate 5 g litre⁻¹ and sodium heptane sulphonate 200 mg litre⁻¹ (pH 2.6). Two millilitre of plasma was transferred into a glass centrifuge tube containing the internal standards and mixed with diethyl ether 8 ml:dichloromethane (10:8 v/v). The resultant mixture was shaken for 10 min, then centrifuged at 3000 g for 5 min. The organic phase was transferred to a glass tube and evaporated to dryness at 50 °C. The residue was reconstituted with 200 µl of mobile phase and 20 µl injected into the HPLC column. Separation was achieved using a micro Bondapak C18 column, and detection at 220 nm with a flow rate of 2 ml min⁻¹ using a Waters HPLC isocratic system. The method was linear for concentrations in the range 0–4 mg litre⁻¹ and the sensitivities for amethocaine and BBA were 0.02 mg litre⁻¹ and 0.05 mg litre⁻¹, respectively;

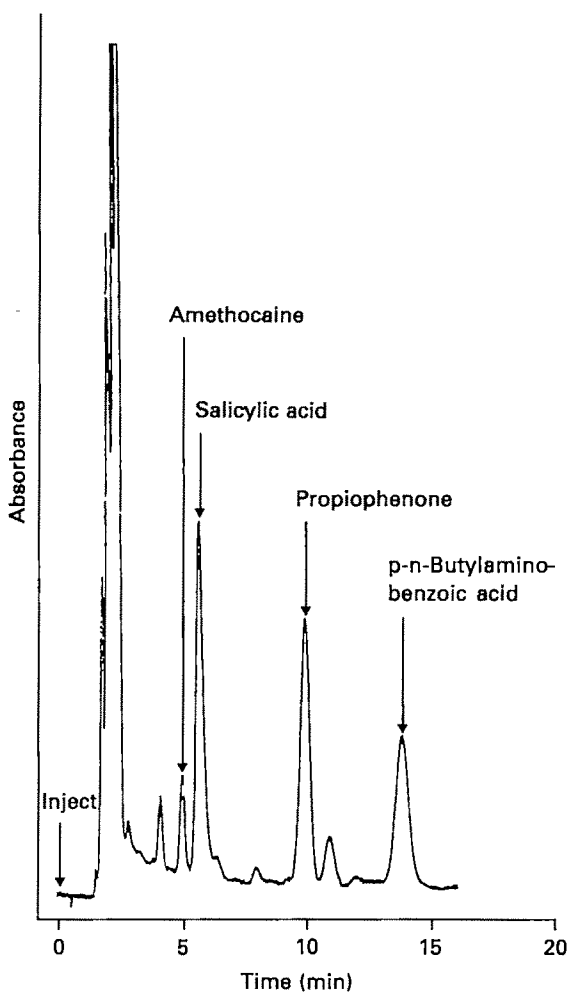


FIG. 1. HPLC chromatograph of the analysis of amethocaine and p-n-butylaminobenzoic acid including their respective internal standards, salicylic acid and propiophenone.

the coefficient of variation was 12.1% for amethocaine and 9.5% for BBA. Recovery rates for amethocaine in plasma containing the sodium metabisulphite and sodium hydroxide were tested by spiking 10-ml blood samples from seven subjects with a known amount of amethocaine. Mean recovery from these control samples was 99% with a coefficient of variation of 13.8%. A typical HPLC profile is shown in figure 1.

RESULTS

Plasma concentrations of amethocaine and BBA are presented in tables I and II, respectively. No amethocaine or BBA was detected in subjects Nos

TABLE I. Plasma concentrations of amethocaine. *nd* = Not detected; *nt* = sample not taken

Subject No.	Amethocaine concn (mg litre ⁻¹)				
	30 min	60 min	120 min	240 min	360 min
1	0.06	0.06	0.02	0.06	nt
2	0.03	0.13	0.02	0.02	nt
3	nd	nd	nd	nd	nt
4	nd	nd	nd	nd	nd
5	nd	nd	nd	nd	nd
6	nd	nd	nd	nd	nd
7	nd	nd	nd	nd	nd
8	nd	nd	nd	nd	nd
9	0.16	0.12	0.14	0.18	0.20
10	nd	nd	nd	nd	nd

TABLE II. Plasma concentrations of *p*-*n*-butylaminobenzoic acid (BBA). *nd* = Not detected; *nt* = sample not taken

Subject No.	BBA concn (mg litre ⁻¹)				
	30 min	60 min	120 min	240 min	360 min
1	nd	nd	nd	nd	nt
2	nd	nd	nd	nd	nt
3	nd	nd	nd	nd	nt
4	0.82	0.30	0.34	0.24	0.20
5	nd	nd	nd	nd	nd
6	nd	nd	nd	nd	nd
7	nd	nd	nd	nd	nd
8	nd	nd	nd	nd	nd
9	nd	nd	nd	nd	0.46
10	nd	nd	nd	nd	nd

3, 5, 6, 7, 8 and 10. In subject No. 4, no amethocaine was found in plasma, but progressively decreasing concentrations of BBA were measured. Amethocaine was detected in plasma in subjects Nos 1, 2 and 9, and in addition BBA was detected at 360 min in subject No. 9.

Pain scores were 0 (no pain) in all subjects. No cardiovascular or neurological side effects were observed. Erythema at the site of application of the cream was associated with itching on removal of the cream in four subjects. This lasted a few hours and resolved without treatment.

DISCUSSION

McCafferty and colleagues have suggested that an amethocaine formulation is the most promising topical dermal anaesthetic agent for use before venepuncture [1]. However, the safety of topically applied amethocaine has been questioned, after several reports of fatal and severe non-fatal toxic

reactions [6-8]. In the cases reported, toxicity occurred most frequently after topical application to mucous membranes before endoscopic instrumentation. Bonica suggested that the potent vasodilator properties of amethocaine enhanced systemic absorption of the drug and this, combined with the high doses used, increased the possibility of toxic reactions [8].

When amethocaine cream is applied to the intact skin, compared with mucous membranes, both the speed and degree of systemic absorption are greatly reduced. Small and colleagues failed to detect any amethocaine in plasma after topical application to three adult volunteers, although no details were given about the duration of application or the method of detection [9]. Evidence of poor absorption was reported also after dermal application of amethocaine 700 mg for 30 min to a volunteer (7 ml of 10% solution in dimethyl sulphoxide) by Brechner, who was unable to detect any drug in plasma, despite analgesia adequate for venepuncture [10]. The present study provides further evidence of poor absorption of amethocaine through intact skin. Despite the prolonged application of the maximum recommended dose [11], and a sensitive method of detection, plasma amethocaine was measurable in only three of 10 volunteers, with a maximum plasma concentration of 0.2 mg litre⁻¹. Excellent analgesia was obtained despite low dermal penetration, as the cutaneous nociceptors are situated just below the stratum corneum, approximately 15 µm beneath the skin surface [12].

Slow systemic drug absorption because of poor skin penetration results in a slow increase in plasma concentrations. Scott stated that with slow i.v. infusions of local anaesthetics "the severity of symptoms and signs was dependent upon the speed of infusion: the more rapid the infusion the greater the CNS toxicity" [13]. The same principle should hold for topically applied local anaesthetic agents, so that slow systemic absorption of amethocaine by this route should contribute to the safety of the formulation. In the present study, when amethocaine was detected it was present for the duration of the sampling, indicating continued absorption throughout the duration of application. In addition, it is possible that an amethocaine depot forms in the dermis and this continues to release the drug after its removal from the skin surface. This accounts for detectable concentrations at 360 min in subject No. 9. Although no amethocaine was detected in

seven subjects, it is probable that the drug was present in the plasma, but below the limits of detection of the method described ($0.02 \text{ mg litre}^{-1}$). This is the first report demonstrating measurable plasma concentrations of amethocaine, and the absence of clinical signs and symptoms of toxicity with plasma concentrations up to $0.2 \text{ mg litre}^{-1}$ is worthy of note.

Amethocaine is hydrolysed by non-specific tissue esterases in the dermis, to p-n-butylaminobenzoic acid (BBA) [12]. This hydrolysis is understood poorly and, although usually slow, the speed may vary between individuals. Slow hydrolysis would account for the lack of detectable BBA in subjects Nos 1 and 2, despite the presence of amethocaine in the plasma although, in these, the final samples were taken at 240 min. In subject No. 9, slow hydrolysis produced detectable BBA at 360 min. It is postulated that subject No. 4 had fast hydrolysis of absorbed amethocaine, accounting for measurable concentrations of BBA without detection of amethocaine. This cutaneous metabolism further decreases the potential for toxicity of dermally applied amethocaine.

The only side effect observed in this study was transient erythema with itching occurring after removal of the cream in four subjects, and this resolved without treatment. Erythema was reported to have occurred in 63% of 1155 subjects studied, after topical application of amethocaine cream in children, with a further 0.6% having a local urticarial reaction [14]. The erythema has been shown to be caused by increased perfusion of the cutaneous microcirculation and is a pharmacological property of the drug rather than a side effect of the formulation [15]. Pruritus may be caused by increased blood flow, but the possibility of an allergic reaction to the metabolite BBA must be excluded as the ester group of local anaesthetics produces significantly more allergic reactions than the amide group. This requires further investigation, as does the use of repeated applications of this preparation.

It is interesting to note that the four subjects with erythema and itching also had detectable amethocaine and BBA in plasma. This suggests that microcirculatory vasodilatation increases the degree of systemic absorption. It is not clear why only four subjects demonstrated this phenomenon.

In this preliminary study, we have demonstrated that, after prolonged topical application of the maximum recommended dose of an amethocaine

formulation to the intact skin, systemic absorption did not occur to a degree sufficient to cause toxic symptoms. As there have been no previous studies correlating plasma concentrations with clinical signs of toxicity, we conclude that after slow dermal absorption, plasma concentrations of amethocaine up to $0.2 \text{ mg litre}^{-1}$ are safe in normal adult subjects.

Further evaluation with larger numbers of patients is necessary before the cream can be recommended for general use, and it is the opinion of the authors that smaller doses of amethocaine could be used without loss of its excellent analgesic properties. Furthermore, the drug must not be applied to broken skin surfaces and, as with EMLA [16], suitable precautions must be taken to ensure that the cream is not ingested orally, as this may lead to rapid systemic absorption and possible toxic reactions.

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REFERENCES

1. McCafferty DF, Woolfson AD, McClelland KH, Boston V. Comparative *in vivo* and *in vitro* assessment of the percutaneous absorption of local anaesthetics. *British Journal of Anaesthesia* 1988; 60: 64-69.
2. McCafferty DF, Woolfson AD, Boston V. *In vivo* assessment of percutaneous absorption of local anaesthetic preparation. *British Journal of Anaesthesia* 1989; 62: 17-21.
3. Coley S. Anaesthesia of the skin. *British Journal of Anaesthesia* 1989; 62: 4-5.
4. Yang S, Xue Y, Tian X, Jui M, Xu X, Yu Y. Simultaneous determination of lidocaine, bupivacaine, and tetracaine in human plasma by HPLC. *Yao Hsueh Hsueh Pao* 1984; 19: 611-615.
5. Menon GB, Norris BJ. Simultaneous determination of tetracaine and its degradation product p-n-butylaminobenzoic acid by HPLC. *Journal of Pharmaceutical Sciences* 1981; 5: 569-570.
6. Jackson CA. Amethocaine hydrochloride: Severe toxic effects when used for bronchoscopy. *British Medical Journal* 1949; 1: 99-101.
7. Jenkins AV. Acute convulsive reaction to surface anaesthetic: Treatment by depolarizing muscle relaxant. *British Journal of Anaesthesia* 1962; 34: 61-64.
8. Bonica JJ. Regional anesthesia with tetracaine (amethocaine). *Anesthesiology* 1950; 11: 606-622, 716-729.
9. Small J, Wallace RG, Millar R, Woolfson AD, McCafferty DF. Pain-free cutting of split skin grafts by application of a percutaneous local anaesthetic cream. *British Journal of Plastic Surgery* 1988; 41: 539-543.
10. Brechner VL, Cohen DD, Pretsky I. Dermal anesthesia

- by the topical application of tetracaine base dissolved in dimethyl sulfoxide. *Annals of the New York Academy of Sciences* 1967; 141: 524-531.
11. Atkinson RS, Rushman GB, Lee JA, eds. *A Synopsis of Anaesthesia*, 10th Edn. Bristol: John Wright, 1987; 602.
 12. Woolfson AD, McCafferty DF, McGowan KE. The metabolism of amethocaine by porcine and human skin extracts: influence on percutaneous anaesthesia. *International Journal of Pharmaceutics* 1990; 62: 9-14.
 13. Scott DB. Toxic effects of local anaesthetic agents on the central nervous system. *British Journal of Anaesthesia* 1986; 58: 732-735.
 14. Woolfson AD, McCafferty DF, Boston V. Clinical experiences with a novel percutaneous amethocaine preparation: prevention of pain due to venepuncture in children. *British Journal of Clinical Pharmacology* 1990; 30: 273-279.
 15. Woolfson AD, McCafferty DF, McGowan KG, Boston V. Non-invasive monitoring of percutaneous local anaesthesia using laser Doppler velocimetry. *International Journal of Pharmacology* 1989; 51: 183-187.
 16. James IG. EMLA: Complications. *British Journal of Anaesthesia* 1990; 65: 295.

SYSTEMIC FENTANYL ENHANCES THE SPREAD OF SPINAL ANALGESIA PRODUCED BY LIGNOCAINE

A. FASSOULAKI, C. SARANTOPOULOS AND S. CHONDRELI

SUMMARY

Seventy-one patients undergoing transurethral prostatectomy under spinal anaesthesia were allocated randomly to one of four groups: fentanyl-naloxone (F-Nal), fentanyl-normal saline (F-NS), normal saline-naloxone (NS-Nal), and normal saline-normal saline (NS-NS) group. Twenty minutes after subarachnoid injection of hyperbaric lignocaine 100 mg, we tested the level of spinal analgesia (pinprick sensation) and administered i.v. either fentanyl 100 µg (F-Nal and F-NS groups) or normal saline 2 ml (NS-Nal and NS-NS groups). Ten minutes later, we assessed the new levels of analgesia and administered i.v. either naloxone 0.4 mg (F-Nal and NS-Nal groups) or normal saline 1 ml (F-NS and NS-NS groups). The level of sensory block was reassessed 10 min after the naloxone or normal saline treatment. Ten minutes after i.v. administration of fentanyl or normal saline, the level of analgesia increased in the F-Nal and F-NS groups by 3.98 and 3.78 cm, respectively, and differed significantly compared with the NS-Nal and NS-NS groups (both $P < 0.01$). Forty minutes after spinal block, the decrease in analgesia in the F-Nal group (3.97 cm) differed significantly from that in the other groups ($P < 0.01$). Systemic fentanyl enhanced the spread of analgesia. This enhancement was antagonized by naloxone.

KEY WORDS

Analgesics: fentanyl. Local anaesthetics: lignocaine. Anaesthetic techniques: spinal.

lignocaine block was expected to regress. The present study was designed to evaluate the effect of low doses of systemic fentanyl on the level of spinal analgesia produced by intrathecal lignocaine. The effect of naloxone after administration of either fentanyl or normal saline was investigated also.

PATIENTS AND METHODS

The study was approved by the Local Ethics Committee and informed consent was obtained from all patients.

Seventy-one unpremedicated patients undergoing transurethral resection of prostate (TURP) under spinal anaesthesia were allocated randomly to one of four groups: i.v. fentanyl-naloxone (group F-Nal); i.v. fentanyl-normal saline (group F-NS); i.v. normal saline-naloxone (group NS-Nal); i.v. normal saline-normal saline (group NS-NS). Patients who were receiving tranquilizers and analgesics before operation, or patients with CNS disorders, were excluded from the study.

On arrival of the patient in the operating room, a cannula was inserted into a suitable vein and Ringer Lactate solution administered i.v. Arterial pressure, ECG, heart rate and oxygen saturation were monitored. Oxygen was administered via a Ventimask designed to deliver 35% oxygen.

With the patient in the left lateral position and after subcutaneous infiltration with 2% lignocaine, 5% (100 mg) hyperbaric lignocaine (Xylocaine, Astra, S.G. 1030-1035) 2 ml was

For certain procedures, spinal anaesthesia may be preferred in the elderly [1]. While administering small doses of fentanyl to patients undergoing surgery under spinal anaesthesia, we observed central spread of sensory analgesia and, occasionally, pain relief after operation by the time the

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TABLE I. Patient characteristics (mean (range or SD))

	Fentanyl-naloxone (n = 18)	Fentanyl-normal saline (n = 18)	Normal saline-naloxone (n = 17)	Normal saline-normal saline (n = 18)
Age (yr)	68.9 (58-80)	70.7 (62-80)	72.5 (62-87)	72.0 (66-85)
Weight (kg)	65.7 (10.4)	72.5 (12.5)	73.9 (13.1)	73.4 (9.3)
Height (cm)	166 (7)	167 (5)	167 (10)	170 (7)

TABLE II. Changes to pinprick sensation (mean (SD)) in each group of patients 30 and 40 min after spinal anaesthesia. $P < 0.01$: ** vs normal saline-naloxone and normal saline-normal saline groups; †† vs fentanyl-normal saline, normal saline-naloxone and normal saline-normal saline groups

	Fentanyl-naloxone (n = 18)	Fentanyl-normal saline (n = 18)	Normal saline-naloxone (n = 17)	Normal saline-normal saline (n = 18)
30 min	3.98 (0.87)**	3.78 (0.94)**	-0.17 (0.23)	-0.26 (0.73)
40 min	-3.97 (0.92)††	-0.41 (0.40)	-0.81 (0.95)	-0.79 (0.80)

injected intrathecally at the L3-4 interspace. All patients remained in the left lateral position for 1 min, after which they were placed in the lithotomy position.

Twenty minutes after the intrathecal injection, the level of analgesia was assessed by a blinded observer. Pinprick sensation was assessed using a 21-gauge needle in a cephalad to caudad direction. To assess the level of analgesia, we defined four points on the posterior, middle and anterior axillary lines of the left abdominal wall, and on the line 5 cm medial to the anterior axillary line, above which patients experienced sensation to pinprick. Changes in the level of spinal analgesia were measured in cm because of difficulty in locating dermatomes in patients in the lithotomy position.

After the spread of spinal analgesia was assessed, 2 ml of a solution of either fentanyl 100 µg (groups F-Nal and F-NS) or normal saline was administered i.v. Changes to pinprick sensation were noted 10 min later (30 min after intrathecal injection) and either naloxone 1 ml (0.4 mg) (groups F-Nal and NS-Nal) or normal saline 1 ml (groups F-NS and NS-NS) was injected i.v. Ten minutes later (40 min after the intrathecal injection), the level of analgesia was reassessed.

The level of analgesia defined 20 min after subarachnoid injection of lignocaine was taken as the baseline level and changes in the level following either fentanyl or normal saline administration were measured in cm. This level was

then redefined as zero and the changes after administration of either naloxone or normal saline were measured. The overall change in the level of sensory block in each group of patients at 30 and 40 min after spinal anaesthesia was calculated by averaging the changes observed in the height of each of the four points lying on the predetermined lines.

A factorial analysis of variance with repeated measures design was used for comparisons of changes in levels of analgesia between groups. When a statistically significant difference was found, Scheffé's method was applied to evaluate comparisons between individual groups.

RESULTS

The four groups were similar in age, weight and height (table I).

A significant difference between the groups in changes to pinprick sensation was found 10 min after the i.v. administration of either fentanyl or normal saline ($F = 175.5$ with 3,67 d.f. and $P < 0.01$). The F-Nal and F-NS groups reported a similar mean increase in cephalad spread of sensory analgesia (table II). This increase corresponded to 1.5 spinal segments and differed significantly compared with the changes reported by patients in the NS-Nal and NS-NS groups. No significant changes occurred in the NS-Nal or NS-NS groups (table II).

Ten minutes after i.v. administration of either naloxone or normal saline, changes in spinal

analgesia to pinprick were significantly different between groups ($F = 77.1$ with 3,67 d.f. and $P < 0.01$). Groups F-NS, NS-Nal and NS-NS reported minor decreases. In the F-Nal group, administration of naloxone resulted in a mean reduction in the level of analgesia of 3.97 cm (table II). This decrease was significant compared with the decreases in the three other groups ($P < 0.01$).

DISCUSSION

The results of the present study show that fentanyl, administered i.v., increased the cephalad spread of sensory analgesia produced by intrathecal lignocaine. This effect was antagonized by naloxone. After the systemic administration of normal saline, naloxone had no effect on the spread of spinal analgesia.

The mechanism of this interaction between systemic fentanyl and intrathecal lignocaine administration is not clear. Systemic fentanyl may affect the intrathecally injected lignocaine indirectly by altering spinal cord blood flow. Systemic morphine has been shown to decrease spinal blood flow [2]. This may reduce absorption of local anaesthetic, increasing the duration rather than the spread of sensory block. However, it is obvious from the NS-Nal and NS-NS groups that the fixation of hyperbaric lignocaine in spinal regions was complete by 20 min. Therefore, changes in spinal cord flow is not likely to affect the spread of sensory block.

The spread of analgesia which followed administration of fentanyl did not occur in the NS-Nal and NS-NS groups. This eliminates the possibility of continued mixing or non-fixation of the lignocaine in the subarachnoid space.

Neither intrathecal morphine 0.2–0.4 mg [3], nor extradural fentanyl [4, 5], modify the analgesic block produced by intrathecal or extradural bupivacaine, respectively. However, the onset and duration of effect of i.v. alfentanil differed significantly compared with alfentanil administered intrathecally [6].

It is conceivable that subclinical analgesia above the level of complete analgesia produced by subarachnoid lignocaine might be potentiated and become clinically detectable by small doses of systemic fentanyl. However, this mechanism is

unlikely, because of the low dose of fentanyl administered.

Opioid receptors may act also at supraspinal sites, altering pain processing at supraspinal level or modulating spinal function [7]. Fentanyl may act in a manner similar to morphine and disinhibit the off-cell, a class of neurone in the rostral ventromedial medulla. These off-cells are involved in pain modulation and their disinhibition by morphine contributes to the analgesic effect of this drug [8].

From our data, it is not possible to distinguish between a change in spinal level and a change in the patient's perception of pain. Assessment of temperature block might be helpful in resolving this issue, but our patients, although co-operative in determining pinprick sensation, were not willing to co-operate in temperature testing.

To our knowledge, neither the interaction of systemic fentanyl and intrathecal lignocaine nor its antagonism by naloxone has been reported previously. Our findings may possess clinical importance, as low doses of systemic fentanyl have a potential role in enhancing spinal analgesia.

REFERENCES

1. Chung F, Meier R, Lautenschlager E, Carmichael FJ, Chung A. General or spinal anesthesia: Which is better in the elderly? *Anesthesiology* 1987; 67: 422–427.
2. Matsumiya N, Dohi S. Effects of intravenous or subarachnoid morphine on cerebral and spinal cord hemodynamics and antagonism with naloxone in dogs. *Anesthesiology* 1983; 59: 175–181.
3. Kalso E. Effects of intrathecal morphine, injected with bupivacaine, on pain after orthopaedic surgery. *British Journal of Anaesthesia* 1983; 55: 415–422.
4. Rucci FS, Cardamone M, Migliori P. Fentanyl and bupivacaine mixtures for extradural block. *British Journal of Anaesthesia* 1985; 57: 275–284.
5. Cohen SE, Tan S, Albright GA, Halpern J. Epidural fentanyl/bupivacaine mixtures for obstetric analgesia. *Anesthesiology* 1987; 67: 403–407.
6. Matsumoto M, Collins JE, Kitahata LM, Yuge O, Tanaka A. A comparison of the effects of alfentanil applied to the spinal cord and intravenous alfentanil on noxious evoked activity of dorsal horn neurons in the cat spinal cord. *Anesthesia and Analgesia* 1986; 65: 145–150.
7. Yaksh TL. Multiple opioid receptor systems in brain and spinal cord: Part 2. *European Journal of Anaesthesiology* 1984; 1: 201–243.
8. Fields HL, Vanegas H, Hentall ID, Zorman G. Evidence that disinhibition of brain stem neurones contributes to morphine analgesia. *Nature (London)* 1983; 306: 684–686.

EFFECT OF P_{aCO_2} ON CEREBRAL BLOOD FLOW DISTRIBUTION DURING HALOTHANE COMPARED WITH ISOFLURANE ANAESTHESIA IN THE RAT

W. L. YOUNG, A. I. BARKAI, I. PROHOVNIK, H. NELSON AND M. DURKIN

SUMMARY

In order to examine anaesthetic effects on the distribution of cerebral blood flow (CBF) during normo- and hypocapnia, male adult Sprague-Dawley rats were allocated randomly to four groups in a 2×2 factorial design, using P_{aCO_2} value and anaesthetic agent as between-group factors. Animals were anaesthetized with either 1.38% isoflurane (inspired) or 1.05% halothane (inspired) and the lungs ventilated mechanically at either normocapnia (P_{aCO_2} 5.1–5.6 kPa) or hypocapnia (P_{aCO_2} 3.1–3.3 kPa) for 1 h. CBF was measured using ^{14}C -iodoantipyrine autoradiography. Local CBF in selected cortical and subcortical regions of interest and area-weighted mean global CBF were calculated. Data were compared by analysis of variance. Normocapnic (mean (SE)) CBF for halothane ($n = 6$) and isoflurane ($n = 7$) was 120 (8) ml/100 g min⁻¹ (P_{aCO_2} 5.6 (0.49) kPa) and 117 (9) ml/100 g min⁻¹ (P_{aCO_2} 5.4 (0.5) kPa), respectively. Hypocapnic CBF for halothane ($n = 6$) and isoflurane ($n = 6$) was 82 (7) ml/100 g min⁻¹ (P_{aCO_2} 3.3 (0.12) kPa) and 82 (6) ml/100 g min⁻¹ (P_{aCO_2} 3.2 (0.12) kPa), respectively. Hypocapnia reduced global CBF for both groups by 30% ($P < 0.001$), but there was no difference between anaesthetic agents ($P > 0.8$). Hypocapnia decreased CBF in all local structures examined. Although subcortical structures had similar CBF at both normocapnia and hypocapnia, CBF in three cortical samples was greater ($P < 0.05$) in both the normocapnic and hypocapnic halothane groups than the corresponding isoflurane groups. The CBF reactivity to changes in P_{aCO_2} was similar for both agents (approximately 2 ml/100 g min⁻¹ mm Hg). We

conclude that halothane is a selective cortical vasodilator compared with isoflurane, but both agents have similar effects on global CBF and local and global CBF reactivity to changes in P_{aCO_2} .

KEY WORDS

Anaesthetics, volatile: halothane, isoflurane. Brain: regional cerebral blood flow. Carbon dioxide: hypocapnia.

Halothane and isoflurane are commonly used anaesthetic agents with different effects on cerebral haemodynamics. In particular, isoflurane produces smaller increases in intracranial pressure (ICP) in neurosurgical patients than halothane, especially in the presence of hypocapnia [1], although it is clear that isoflurane may cause increased ICP in some patients [2]. However, the mechanism of the different effect on ICP is not clear, as halothane and isoflurane produce variable effects on cerebral blood flow, depending on the method of measurement [3]. There is evidence that both agents have a similar effect on total cerebral blood volume [4]. Halothane has been described as being a selective cortical vasodilator relative to isoflurane [3]; however, the effect of P_{aCO_2} on this distribution is not known. This knowledge would be useful and may have implications for the use of induced hypocapnia in focal cerebral ischaemia [5]. This study has examined the influence of P_{aCO_2} on the dis-

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tribution of cerebral blood flow (CBF) during halothane compared with isoflurane anaesthesia.

MATERIALS AND METHODS

Male adult Sprague-Dawley rats were allocated randomly to four groups in a 2×2 factorial design, using two P_{aCO_2} values and two anaesthesia groups. Animals were anaesthetized with 1 MAC of either 1.38% isoflurane (inspired) or 1.05% halothane (inspired) and the lungs ventilated mechanically to achieve either normocapnia (P_{aCO_2} 5.1–5.6 kPa) or hypocapnia (P_{aCO_2} 3.1–3.3 kPa).

Animals were allowed free access to food and water before all experiments. Anaesthesia was induced in a breathing chamber with the appropriate volatile agent. The trachea was cannulated with PE-240 tubing and ventilation was controlled with a Harvard rodent ventilator (Harvard Instruments, South Natick, MA, U.S.A.) using air and supplementary oxygen. Methyltubocurarine iodide 0.1 mg kg^{-1} , was given i.v. to produce neuromuscular block. Cannulae were placed in both femoral arteries and veins. Arterial pressure was recorded continuously on a Grass model 7 polygraph (Grass, Inc., Quincy, MA, U.S.A.). Temperature was maintained at 37°C using a heating lamp and monitored by rectal thermistor. Heparin 50 iu was given i.v.

P_{aCO_2} was verified by arterial blood-gas measurements. After 1 h of mechanical ventilation, CBF was determined by the ^{14}C -iodoantipyrine indicator fractionation method [6–8] and autoradiographic densitometric analysis [3, 9]. A bolus of ^{14}C -iodoantipyrine $20 \mu\text{Ci kg}^{-1}$ (New England Nuclear, Boston, MA, U.S.A.) in 0.9% saline 0.3 ml was given i.v., with simultaneous withdrawal of a reference flow sample from a femoral artery catheter using a Harvard Pump (Harvard Instruments, South Natick, MA, U.S.A.) set at a rate of $0.393 \text{ ml min}^{-1}$. After 10 s the experiment was terminated by decapitation of the rat and the reference flow arterial catheter was withdrawn simultaneously from the femoral artery. The brain was removed quickly and frozen. Blood obtained from the 10-s withdrawal from the femoral artery for reference flow activity was decolorized. Blood radioactivities were assessed by liquid scintillation counting using a Packard Tricarb counter (Packard Instrument Co., Sterling VA, U.S.A.).

Using a cryostat at -20°C , the frozen brains were cut into $20\text{-}\mu\text{m}$ coronal sections at intervals

of $240 \mu\text{m}$. Sections for each brain were mounted on glass slides and dried on a hot plate. The slides were exposed to Kodak SB-5 autoradiographic film for 1 week together with ^{14}C -methylmethacrylate standards (Amersham Inc., Arlington Heights, IL, U.S.A.). A digital densitometer (RAS 1000 Research Analysis System, Amersham, Inc.) was used to produce optical density images. Using tissue optical densities, the carbon-14 standards and the reference blood flow radioactivity data, CBF was calculated as described previously [7–9]. "Global CBF" was calculated using a modification of the method described by Hansen and colleagues [3] using area-weighted averages of CBF from six cut sections distributed equally along the rostral-caudal axis of the brain at the level of frontal cortex, caudoputamen, thalamus, substantia nigra, inferior colliculus and cerebellum. (The six section levels correspond to co-ordinates taken from the figure by Paxinos and Watson [10]—bottom of figure 50, lateral 2.9-mm sagittal section of rat brain: $-2, 1, 3.5, 6, 9.5$ and 11.5 .) Local CBF was calculated in selected cortical and subcortical regions of interest.

CBF values for all groups were compared by three-way multivariate analysis of variance (ANOVA) using anaesthetic (halothane *vs* isoflurane) and ventilation (normocapnia *vs* hypocapnia) as between-group factors and brain region as a repeated measure. Significance levels were adjusted by the Huynh-Feldt sphericity correction. Other physiological data were compared using a similar two-way ANOVA without the region factor. *Post hoc* comparisons to localize the differences detected by a significant ANOVA were made using the Fisher Protected Least Significant Differences test. Data are reported as mean (SE).

RESULTS

The pH and P_{aCO_2} values were appropriately different between ventilation groups, but similar for halothane- and isoflurane-anaesthetized animals (table I). Mean arterial pressure was 20% less for halothane-anaesthetized animals ($P < 0.001$) and the isoflurane-hypocapnia group had a greater mean arterial pressure than the normocapnic group, although all values were within the autoregulatory range [11]. Hypocapnia reduced area-weighted global CBF for both groups by 30% ($P < 0.001$), but there was no difference

TABLE I. Physiological variables obtained at the time of determination of rCBF (mean (SE)). Significant effects: * anaesthetic; † hypocapnia; § interaction. ¶ Isoflurane significantly greater than halothane during hypocapnia

	Normocapnia		Hypocapnia		ANOVA
	Halothane (n = 6)	Isoflurane (n = 7)	Halothane (n = 6)	Isoflurane (n = 6)	
pH	7.37 (0.05)	7.37 (0.02)	7.53 (0.02)	7.55 (0.02)	†
Pa _{CO₂} (kPa)	5.6 (0.49)	5.4 (0.15)	3.3 (0.12)	3.2 (0.12)	†
Pa _{O₂} (kPa)	21.1 (2.13)	14.9 (1.2)	22.5 (1.87)	26.3 (1.73)	†§
Mean arterial pressure (mm Hg)	72 (6)	80 (2)	67 (4)	94 (4)	*§¶
Plasma glucose (mg dl ⁻¹)	191 (14)	193 (14)	185 (27)	160 (10)	

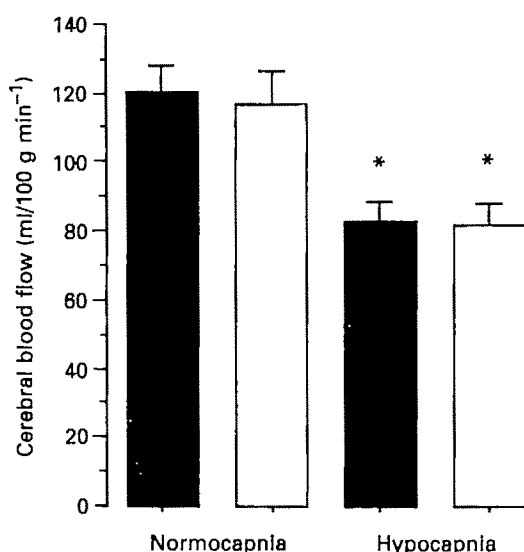


FIG. 1. Comparison of area-weighted mean global CBF for halothane (■) and isoflurane (□) groups during normo- and hypocapnia (mean, SE). * Significantly different from normocapnia ($P < 0.05$).

between anaesthetic agents ($P > 0.8$) (fig. 1). There was a significant effect of Pa_{CO_2} value to decrease CBF in all six brain sections used for the calculation of the area-weighted global value (fig. 2), however, there were significant differences between anaesthetic groups only in the first section value in the two normocapnic groups and the sixth section value in the two hypocapnic groups.

Hypocapnia decreased local CBF in all local structures examined (table II). A lack of significant ventilation-by-anaesthetic interactions, either second or third order, suggests that there was no differential anaesthetic effect on carbon dioxide reactivity, which was similar

for both agents (approximately 2 ml/100 g min⁻¹ mm Hg). The region-by-anaesthetic interaction ($P < 0.0001$) was tested by univariate ANOVA on each region. Although subcortical structures had similar CBF at both normocapnia and hypocapnia, local CBF in the three cortical samples was greater in both the normocapnic and hypocapnic halothane groups than in the corresponding isoflurane groups (table II). All other regions showed the opposite trend: CBF tended to be greater with isoflurane than with halothane. Only in the inferior colliculus did this reversal reach significance ($P < 0.0001$), where isoflurane CBF was approximately two-fold greater than that for halothane.

DISCUSSION

This study has confirmed that halothane is a selective cortical vasodilator and demonstrates that this effect was present during both normo- and hypocapnia. Furthermore, the degree of hypocapnic reduction of CBF with both agents was similar in both cortical and subcortical structures.

There have been several reports on the effects of halothane and isoflurane on CBF in both animals [11–18] and humans [19–28]. There is debate on the relative effects of one agent compared with the other as far as relative vasodilating properties. This issue was reconciled partly by the report from Hansen and colleagues that, during normocapnia, halothane selectively dilated cortical but not subcortical structures relative to isoflurane. However, “whole-brain” CBF did not differ between the two agents [3]. They suggested that the CBF methodology chosen may determine whether or not one observes a difference between the two agents.

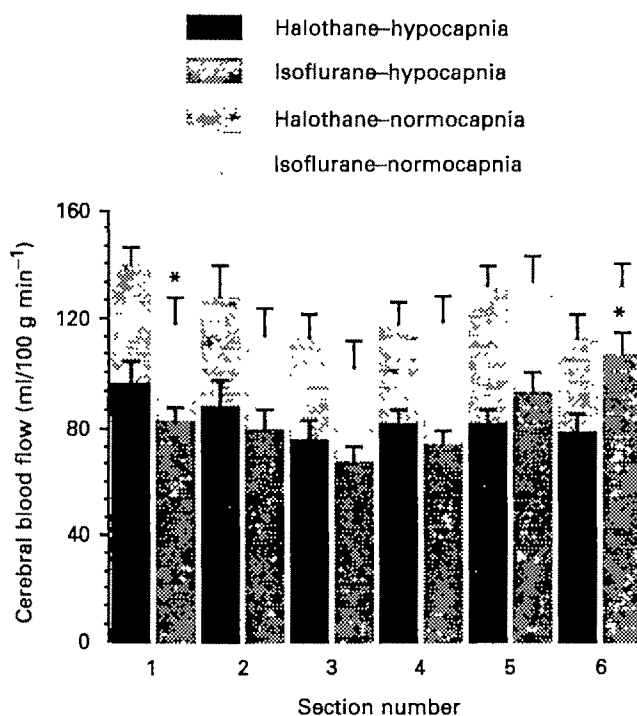


FIG. 2. Comparison of CBF from brain sections 1-6 for halothane and isoflurane during normo- and hypocapnia (mean, SE). There was a significant effect of P_{aCO_2} value to decrease CBF in all sections. There were significant differences between anaesthetic groups only in the first section value in the two normocapnic groups and the sixth section value in the two hypocapnic groups. * Significantly different from halothane group at the same section level ($P < 0.05$).

TABLE II. Local CBF ($ml/100\text{ g min}^{-1}$) in cortical and subcortical regions (mean (SE)). Significant effects: * anaesthetic; † hypocapnia

	Normocapnia		Hypocapnia		ANOVA
	Halothane (n = 6)	Isoflurane (n = 7)	Halothane (n = 6)	Isoflurane (n = 6)	
Frontal cortex	153 (8)	119 (12)	119 (12)	82 (7)	**†
Motor cortex	162 (14)	121 (15)	115 (15)	85 (6)	**†
Sensory cortex	148 (12)	113 (14)	110 (13)	91 (6)	**†
Corpus callosum	56 (7)	61 (5)	43 (4)	46 (3)	†
Caudoputamen	155 (12)	132 (13)	112 (13)	91 (9)	†
Hippocampus	102 (11)	112 (9)	72 (5)	72 (6)	†
Hypothalamus	105 (12)	113 (9)	65 (6)	67 (7)	†
Thalamus	106 (10)	113 (14)	74 (6)	62 (5)	†
Inferior colliculus	148 (15)	234 (12)	111 (15)	184 (17)	**†
Cerebellum	105 (8)	105 (8)	75 (6)	87 (6)	†

These authors also studied the flow-metabolism coupling during isoflurane or halothane anaesthesia and found that isoflurane selectively depressed cortical metabolism; they speculated that this was the cause of the relative vasodilatation by halothane in cortex [29]. Our results indirectly

support their observations and assumptions. In our study there appeared to be no differential effect of one agent on carbon dioxide reactivity. As modest hypocapnia should not affect cerebral metabolic rate [30], if one assumes that the differing effects of halothane and isoflurane are

caused by effects on local metabolic rates, one would postulate that manipulation of cerebrovascular resistance by hypocapnia would not alter flow distribution.

Compared with halothane, isoflurane appears to enhance cortical CBF reactivity to P_{aCO_2} in the cat by intra-arterial xenon-133 washout [15] and in the rabbit by hydrogen clearance [17]. However, using the venous outflow technique, canine global CBF P_{aCO_2} reactivity does not differ for the two agents [13]. There are a large number of studies in humans which have examined P_{aCO_2} reactivity to either isoflurane or halothane [19–21, 24, 25, 27, 28] and one study comparing the agents during carotid endarterectomy [31]. All the human studies have reported quantitatively similar slopes of the carbon dioxide response line, using both cortical-weighted measures (xenon-133 washout) and whole-brain methods (Kety-Schmidt method). Our results suggest that cortical and subcortical carbon dioxide reactivity are similar in the carbon dioxide concentration range examined in this study. However, it should be noted that to compare most accurately quantitative differences in carbon dioxide reactivity for cortical and subcortical structures, one should use a repeated-measure CBF design for assessing individual subject reactivity, rather than looking at a slope of group means. Repeated measures of CBF is not possible at present with autoradiographic CBF determination. However, using data derived from the experimental design in our present study, it can be concluded that there is no effect of hypocapnia on the pattern of cortical *vs* subcortical flow distribution with the two agents.

Our reported values for global CBF should be interpreted cautiously, as the area-weighted method of estimating global CBF may bias the value towards the structures included in the sections used for the calculations. We adapted the method from that described by Hansen and colleagues [3] with the following modification: whereas they selected only forebrain structures that tended to be located centrally, we chose six sections placed approximately equidistant along the rostral-caudal axis of the brain. Despite the different method of choosing sections, our values for whole brain flow are similar. We observed a significant difference in the first (frontal cortex) section between halothane and isoflurane (although only at normocapnia), and attributed this to the preponderance of cortex in the sample.

A surprising observation was that hindbrain values for CBF were greater with isoflurane than for halothane. The same was true for one of the more caudal local structures we examined, inferior colliculus. Hansen's group did not examine hindbrain, but found no difference in inferior colliculus local CBF [3]. However, Maekawa and colleagues [16] described CBF distribution at different MAC multiples of isoflurane and, for 1 MAC isoflurane, reported CBF values for inferior colliculus and frontal cortex of 267 and 149 ml/100 g min⁻¹, giving a ratio of 1.8, comparable to our ratio of 2.0 for the same structures. Mohamed and colleagues [32] used a rat preparation anaesthetized with 1.0% halothane to evaluate the effect of nimodipine on flow-metabolism coupling. In their vehicle-treated control group, they reported values for inferior colliculus and frontal cortex of 230 and 179 ml/100 g min⁻¹, giving a ratio of 1.3, comparable to our ratio of 1.0. Although we know of no other published reports that compare directly the effects of halothane and isoflurane in caudal structures, there is some evidence that this differential effect between agents has been suggested previously. Although we have no good explanation for this selective effect of isoflurane, it is related presumably to a hindbrain metabolic effect.

Although, in animal studies of neurological outcome after incomplete regional [33] or focal [34] ischaemia, no difference exists between the influence of isoflurane and halothane, isoflurane has been associated with fewer ischaemic EEG changes during carotid endarterectomy than halothane [35, 36]. Therefore, the issue of whether or not isoflurane affords some degree of cerebral protection relative to halothane remains to be resolved. Regardless of the baseline differences in relative amounts of vasodilatation, differences in CBF reactivity to carbon dioxide could affect the clinical management of patients at risk for development of intraoperative cerebral ischaemia, such as during carotid endarterectomy. The use of induced hypocapnia may be beneficial when applied during the acute development of cerebral ischaemia during general anaesthesia [5]. We conclude that, in the rat, halothane is a selective cortical vasodilator and this effect is present at both normo- and hypocapnia. Furthermore, halothane and isoflurane have similar effects on cerebral carbon dioxide reactivity. The use of hypocapnia to promote "inverse steal" in the

presence of cerebral ischaemia should be effective with both agents.

REFERENCES

- Adams RW, Cucchiara RF, Gronert GA, Messick JM, Michenfelder JD. Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. *Anesthesiology* 1981; 54: 97-99.
- Grosslight K, Foster R, Colohan AR, Bedford RF. Isoflurane for neuroanesthesia: Risk factors for increases in intracranial pressure. *Anesthesiology* 1985; 63: 533-536.
- Hansen TD, Warner DS, Todd MM, Vust LJ, Trawick DC. Distribution of cerebral blood flow during halothane versus isoflurane anesthesia in rats. *Anesthesiology* 1988; 69: 332-337.
- Katz JJ, Todd MM, Warner DS. Quantitative comparison of cerebral blood volume in rats receiving halothane or isoflurane. *Anesthesiology* 1988; 69: A534.
- Artru AA, Merriman HG. Hypocapnia added to hypertension to reverse EEG changes during carotid endarterectomy. *Anesthesiology* 1989; 70: 1016-1018.
- Patlak CS, Blasberg RG, Fenstermacher JD. An evaluation of errors in the determination of blood flow by the indicator fractionation and tissue equilibration (Kety) methods. *Journal of Cerebral Blood Flow and Metabolism* 1984; 4: 47-60.
- Young WL, Josovitz K, Morales O, Chien S. The effect of nimodipine on post-ischemic cerebral glucose utilization and blood flow in the rat. *Anesthesiology* 1987; 67: 54-59.
- Young WL, Chien S. Effect of nimodipine on cerebral blood flow and metabolism in rats during hyperventilation. *Stroke* 1989; 20: 275-280.
- Young WL, Barkai A, Prohovnik I, Nelson H, Durkin M. Nimodipine does not increase cerebral blood flow during hypocapnia in the rat. *Journal of Neurosurgical Anesthesiology* 1990; 2: 284-289.
- Paxinos G, Watson C. Figure 50. In: *The Rat Brain: A Stereotactic Atlas*. New York: Academic Press, 1982.
- Todd MM, Drummond JC. A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. *Anesthesiology* 1984; 60: 276-282.
- Theye RA, Michenfelder JD. The effect of halothane on canine cerebral metabolism. *Anesthesiology* 1968; 29: 1113-1118.
- Cucchiara RF, Theye RA, Michenfelder JD. The effects of isoflurane on canine cerebral metabolism and blood flow. *Anesthesiology* 1974; 40: 571-574.
- Stullken EH jr, Milde JH, Michenfelder JD, Tinker JH. The nonlinear responses of cerebral metabolism to low concentrations of halothane, enflurane, isoflurane, and thiopental. *Anesthesiology* 1977; 46: 28-34.
- Drummond JC, Todd MM. The response of the feline cerebral circulation to Pa_{CO}, during anesthesia with isoflurane and halothane and during sedation with nitrous oxide. *Anesthesiology* 1985; 62: 268-273.
- Maekawa T, Tommasino C, Shapiro HM, Keifer-Goodman J, Kohlenberger RW. Local cerebral blood flow and glucose utilization during isoflurane anesthesia in the rat. *Anesthesiology* 1986; 65: 144-151.
- Scheller MS, Todd MM, Drummond JC. Isoflurane, halothane, and regional cerebral blood flow at various levels of Pa_{CO}, in rabbits. *Anesthesiology* 1986; 64: 598-604.
- McPherson RW, Brian JE, Traystman RJ. Cerebrovascular responsiveness to carbon dioxide in dogs with 1.4% and 2.8% isoflurane. *Anesthesiology* 1989; 70: 843-850.
- Wollman H, Alexander SC, Cohen PJ, Chase PE, Melman E, Behar MG. Cerebral circulation of man during halothane anesthesia: Effects of hypocarbia and of d-tubocurarine. *Anesthesiology* 1964; 25: 180-184.
- McHenry L, Slocum H, Bivens HE, Mayes HA, Hayes GJ. Hyperventilation in awake and anesthetized man. *Archives of Neurology* 1965; 12: 270-277.
- Waltz AG, Sundt TM, Michenfelder JD. Cerebral blood flow during carotid endarterectomy. *Circulation* 1972; 45: 1091-1096.
- Sundt TM, Sharbrough FW, Piepgras DG, Kearns TP, Messick JM, O'Fallon WM. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy. *Mayo Clinic Proceedings* 1981; 56: 533-543.
- Eintrei C, Lesznowski W, Carlsson C. Local application of ¹³³xenon for measurement of regional cerebral blood flow (rCBF) during halothane, enflurane, and isoflurane anesthesia in humans. *Anesthesiology* 1985; 63: 391-394.
- Madsen JB, Cold GE, Hansen ES, Bardrum B. The effect of isoflurane on cerebral blood flow and metabolism in humans during craniotomy for small supratentorial cerebral tumors. *Anesthesiology* 1987; 66: 332-336.
- Madsen JB, Cold GE, Hansen ES, Bardrum B. Cerebral blood flow, cerebral metabolic rate of oxygen and relative CO₂-reactivity during craniotomy for supratentorial cerebral tumours in halothane anaesthesia: A dose-response study. *Acta Anaesthesiologica Scandinavica* 1987; 31: 454-457.
- Young WL, Prohovnik I, Correll JW, Ornstein E, Matteo RS, Ostapovich N. Cerebral blood flow and metabolism in patients undergoing anesthesia for carotid endarterectomy: A comparison of isoflurane, halothane, and fentanyl. *Anesthesia and Analgesia* 1989; 68: 712-717.
- Young WL, Prohovnik I, Correll JW, Ostapovich N, Ornstein E, Matteo RS, Baker KZ. A comparison of the cerebral hemodynamic effects of sufentanil and isoflurane in humans undergoing carotid endarterectomy. *Anesthesiology* 1989; 71: 863-869.
- Young WL, Prohovnik I, Ornstein E, Ostapovich N, Sisti MB, Solomon RA, Stein BM. The effect of arteriovenous malformation resection on cerebrovascular reactivity to carbon dioxide. *Neurosurgery* 1990; 27: 257-267.
- Hansen TD, Warner DS, Todd MM, Vust LJ. The role of cerebral metabolism in determining the local cerebral blood flow effects of volatile anesthetics: Evidence for persistent flow-metabolism coupling. *Journal of Cerebral Blood Flow and Metabolism* 1989; 9: 323-328.
- Pierce EC, Lambertson CJ, Deutsch S, Chase PE, Linde HW, Dripps RD, Price HL. Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. *Journal of Clinical Investigation* 1962; 41: 1664-1671.
- Young WL, Prohovnik I, Correll JW, Ostapovich N, Ornstein E, Quest DO. Cerebral blood flow reactivity to CO₂ during halothane or isoflurane anesthesia for carotid endarterectomy. *Anesthesiology* 1990; 73: A204.
- Mohamed AA, Mendelow AD, Teasdale GM, Harper AM, McCulloch J. Effect of the calcium antagonist

- nimodipine on local cerebral blood flow and metabolic coupling. *Journal of Cerebral Blood Flow and Metabolism* 1985; 5: 26-33.
33. Baughman VL, Hoffman WE. Neurologic outcome in rats following incomplete cerebral ischemia during halothane, isoflurane, or N₂O. *Anesthesiology* 1988; 69: 192-198.
34. Gelb AW, Boisvert DP, Tang C, Lam AM, Marchak BE, Dowman R, Mielke BW. Primate brain tolerance to temporary focal cerebral ischemia during isoflurane- or sodium nitroprusside-induced hypotension. *Anesthesiology* 1989; 70: 678-683.
35. Michenfelder JD, Sundt TM, Fode N, Sharbrough FW. Isoflurane when compared to enflurane and halothane decreases the frequency of cerebral ischemia during carotid endarterectomy. *Anesthesiology* 1987; 67: 336-340.
36. Blume WT, Ferguson GG, McNeill DK. Significance of EEG changes at carotid endarterectomy. *Stroke* 1986; 17: 891-897.

INTERACTION BETWEEN BETAMETHASONE AND VECURONIUM

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SUMMARY

A possible interaction between betamethasone and vecuronium was examined in 20 rat phrenic nerve-hemidiaphragm preparations. Ten preparations were bathed in a physiological solution with betamethasone $1 \mu\text{mol litre}^{-1}$ added and, after a 30-min period were exposed to vecuronium at concentrations of 4, 6, 8 and $10 \mu\text{mol litre}^{-1}$ with vecuronium free washings between each exposure. Ten control experiments were performed also using a betamethasone-free bathing solution. In comparison with control, the betamethasone group had significantly ($P = 0.0008$) less depression of muscle contraction (twitch) force at all concentrations of vecuronium. The calculated ED_{50} (50% depression of muscle contraction force) was $5.65 \mu\text{mol litre}^{-1}$ for controls and $7.39 \mu\text{mol litre}^{-1}$ for betamethasone-pretreated preparations. This study confirms our previous clinical observations that an interaction occurs between vecuronium and betamethasone which is characterized by resistance to neuromuscular block.

KEY WORDS

Interactions: betamethasone, vecuronium. Neuromuscular relaxants: vecuronium.

Steroids have been known for several years to facilitate neuromuscular function, and steroid induced resistance to competitive neuromuscular blocking drugs has been noted in three previous case reports [1-3]. Recently we reported two neurosurgical patients treated with betamethasone who had apparent resistance to vecuronium, and in a subsequent review of anaesthesia case records we found that patients treated with betamethasone required on average, 75% more

vecuronium than patients not treated [4]. In this study we have attempted to demonstrate an interaction between betamethasone and vecuronium in a rat phrenic nerve-hemidiaphragm preparation.

MATERIALS AND METHODS

Male Dark Agouti rats (8-10 weeks) weighing 150-200 g were killed by cervical dislocation. The right and left hemidiaphragms with accompanying phrenic nerves were dissected out, placed horizontal in individual Res-Del organ baths and bathed with a physiological solution (RS-1 mammalian solution) aerated with 5% carbon dioxide in oxygen [5]. The composition of the solution is summarized in table I.

The bathing temperature was maintained at $34.5 \pm 0.5^\circ\text{C}$ and the muscle stretched to a basal preload tension of 4 g. Each preparation was attached to an isometric force transducer inserted through the central tendon of the hemidiaphragm and was stimulated indirectly using suction electrodes attached to the phrenic nerve, with a continuous biphasic double pulse (12-ms pulse interval) square wave at a supramaximal voltage of 0.1 ms duration at 0.2 Hz. Short periods (30 s) of direct muscle stimulation (supramaximal monophasic stimulation at 5 Hz) were performed also using muscle electrodes to exclude any local action of betamethasone or vecuronium on the muscle. Contractions were recorded isometrically and displayed on a pen chart recorder.

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TABLE 1. Solute composition and concentration of the physiological solution. BES = *N,N*-bis[2-hydroxyethyl]-2-aminoethanesulphonic acid

Na ⁺ 136.0 mmol litre ⁻¹	Glycerol 0.11 mmol litre ⁻¹
Cl ⁻ 118.0 mmol litre ⁻¹	L-Aspartate 0.02 mmol litre ⁻¹
K ⁺ 5.0 mmol litre ⁻¹	L-Glutamate 0.30 mmol litre ⁻¹
Ca ²⁺ 1.2 mmol litre ⁻¹	L-Glutamine 0.40 mmol litre ⁻¹
Mg ²⁺ 0.45 mmol litre ⁻¹	DL-Carnitine 0.05 mmol litre ⁻¹
HCO ₃ ⁻ 25.0 mmol litre ⁻¹	Choline 0.01 mmol litre ⁻¹
BES 5.0 mmol litre ⁻¹	Coccarboxylase (TTP) 0.043 mmol litre ⁻¹
D-Glucose 10.0 mmol litre ⁻¹	Insulin (porcine) 25 mIU litre ⁻¹

Where possible, the preparations were used in pairs from the same rat, in independently perfused double organ baths with equal numbers of left/right hemidiaphragms used for each group. The flow rate of the perfusate was 2 ml min⁻¹. At least 30 min was allowed for a steady state to be achieved; muscle contraction (twitch) force measurements produced by indirect and direct stimulation of preparations in the absence of steroid or neuromuscular blocker were recorded. One of the hemidiaphragm preparations was exposed to betamethasone 1 µmol litre⁻¹ for the duration of the investigation. All changes of perfusate solution commenced with a 40-ml flush (the volume of the organ bath) followed by perfusate 2 ml min⁻¹. Control and betamethasone treated preparations were exposed to vecuronium at concentrations of 4, 6, 8 and 10 µmol litre⁻¹. Muscle contraction force (both direct and indirect) was recorded 30 min after each change of perfusate containing vecuronium. Vecuronium-free solutions were used to wash the preparations until twitch height returned to control values, at which time the next vecuronium concentration was added.

To ensure that preparations had not deteriorated during the experimental period, data were not included in the analysis if the response to direct stimulation had decreased at the end of the experiment.

Statistics

Data from control and betamethasone groups were compared using analysis of covariance, with the dose of vecuronium as the covariate and terms for the control or betamethasone groups and for individual preparations within these groups. A test for difference in slope between the control group and betamethasone group was made by including a dose × group term in the model.

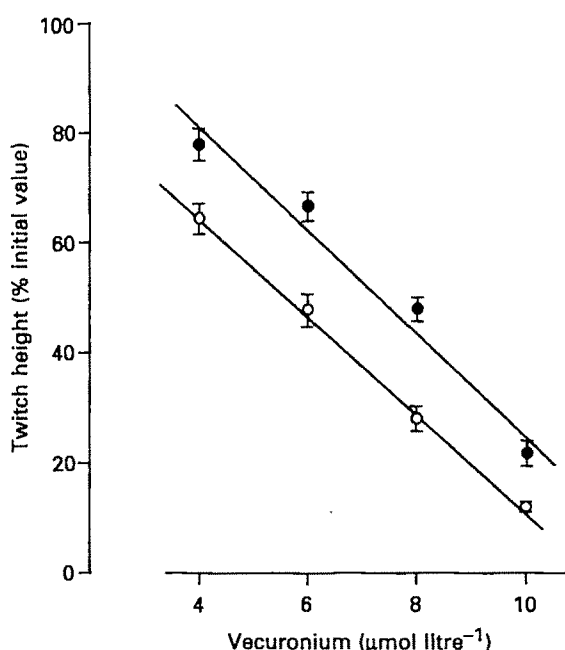


FIG. 1. Dose-response relationship for control (O) and betamethasone-pretreated (●) preparations (mean, SEM). The ED₅₀ for 50% depression of twitch height was 5.65 µmol litre⁻¹ for control and 7.39 µmol litre⁻¹ for betamethasone-pretreated preparations.

RESULTS

Satisfactory data were obtained from 20 hemidiaphragm preparations. Ten received betamethasone and 10 acted as control. No significant difference was observed in indirectly or directly stimulated mean twitch height before and after addition of betamethasone.

The slopes of the dose-response lines to vecuronium in control and betamethasone treated preparations were not significantly different ($P = 0.14$) (fig. 1). When a common slope was fitted, in

comparison with control, the betamethasone group showed significantly ($P = 0.0008$) less depression at all concentrations of vecuronium examined. The calculated ED_{50} for 50% depression of twitch height was $5.65 \mu\text{mol litre}^{-1}$ for controls and $7.39 \mu\text{mol litre}^{-1}$ for betamethasone pretreated preparations. Thus the addition of betamethasone increased the ED_{50} for vecuronium by approximately 30%.

DISCUSSION

In 1944, Torda and Wolff demonstrated that neuronal synthesis of acetylcholine could be increased by prior administration of adrenocorticotrophic hormone (ACTH) [6]. They demonstrated also that, in the absence of ACTH (hypophysectomized rats), there was reduced acetylcholine synthesis resulting in neuromuscular dysfunction, which was restored following administration of ACTH [7].

Recent case reports suggest that an interaction between corticosteroids and the neuromuscular junction may have clinical implications for the anaesthetist. There have been two case reports of partial recovery from pancuronium given in association with steroid therapy [1, 2] and a case of resistance to vecuronium in a patient receiving long-term testosterone [3]. Following two cases of unexpected movement during neurosurgery in patients receiving vecuronium and pretreated with betamethasone, we performed a retrospective review of 50 neurosurgical patients, examining the doses of vecuronium administered to patients with and without betamethasone pretreatment. Those data suggested that patients pretreated with betamethasone were resistant to the neuromuscular blocking properties of vecuronium and required, on average, 75% more blocking drug [4].

Animal studies that have examined the effects of tubocurarine in the presence of glucocorticoids have demonstrated resistance to the effects of the neuromuscular blocker in animals treated with prednisolone [8], dexamethasone [9], betamethasone [10] and triamcinolone [11, 12].

In this study we have demonstrated that the reduction in twitch tension caused by vecuronium was reduced considerably in the presence of betamethasone $1 \mu\text{mol litre}^{-1}$. Although the mechanism of this interaction is not fully understood, previous work suggests several possible

sites where steroids may affect neuromuscular transmission:

(1) *Motor neurone*

Glucocorticoids have been shown to have a direct facilitatory effect at the impulse generating end of the motor nerve axon. In the cat, administration of large doses of methylprednisolone ($8 \text{ mg kg}^{-1} \text{ day}^{-1} \text{ i.m.}$) for 1 week altered the electrical properties of spinal motor neurones and increased the excitability of the initial axon segment, the site of physiological impulse initiation [13].

(2) *The presynaptic nerve terminal*

Experimental work suggests that corticosteroids act presynaptically stimulating the synthesis, spontaneous release and stimulated release of acetylcholine.

(a) *Synthesis of acetylcholine.* The synthesis of acetylcholine is related directly to the supply of extraneural choline, which is transported by a sodium dependent carrier system located at the presynaptic membrane of the nerve terminal. Hemicholinium-3 is a presynaptic inhibitor of this carrier-mediated transport and virtually abolishes the synthesis of acetylcholine. Dexamethasone and prednisolone partially antagonize hemicholinium-3 [14] and increase acetylcholine synthesis *in vitro* by facilitating the uptake of choline and its subsequent incorporation into acetylcholine [15]. Electron micrographs of the neuromuscular junction support corticosteroid enhanced acetylcholine synthesis by revealing increases in the mean size of synaptic vesicles after incubation with prednisolone and dexamethasone [16].

(b) *Spontaneous release of acetylcholine.* Micromolar concentrations of prednisolone and dexamethasone have been shown to increase both the amplitude and frequency [17–19] of miniature end-plate potentials. These observations suggest that corticosteroids facilitate spontaneous release of acetylcholine.

(c) *Stimulated release of acetylcholine.* The application of small concentrations of prednisolone ($1 \mu\text{mol litre}^{-1}$) to the frog neuromuscular junction results in a doubling of nerve evoked end-plate currents. However, if prednisolone is added specifically to the end-plate via a micropipette,

such a response is not observed. This implies that stimulated release of acetylcholine may be augmented by corticosteroids acting at a presynaptic site [20].

(3) Postsynaptic nerve terminal

In the rat, large concentrations of prednisolone ($0.6 \text{ mmol litre}^{-1}$) have a depressant effect on neuromuscular transmission. However, dexamethasone counteracts the suppression of contraction caused by tubocurarine at small concentrations, but this effect is not observed when greater concentrations of steroid are used [9]. It has been suggested, therefore, that the presynaptic facilitatory effects of small concentrations of corticosteroids on acetylcholine release may be overcome by a greater postsynaptic depressant effect at large concentrations [21]. This may explain why some workers have failed to demonstrate any evidence of recovery from tubocurarine after administration of prednisolone [22].

The evidence suggests that the major site of the facilitatory actions of corticosteroids at the neuromuscular junction is prejunctional and it seems feasible that the attenuation of competitive neuromuscular block observed in our study is a consequence of steroid-induced enhancement of acetylcholine synthesis and release.

A prejunctional reduction in release of acetylcholine by vecuronium, in addition to postjunctional receptor block, has been reported using *in vitro* toad neuromuscular preparations [23]. However, conclusions made from *in vitro* neuromuscular preparations investigating presynaptic modulation are limited [24] and the presence of autoregulating presynaptic acetylcholine receptors at the motor end-plate area has been questioned [25]. Perhaps of more clinical relevance are the observations of Baker and his colleagues in anaesthetized cats. They reported a biphasic prejunctional effect of vecuronium; at small concentrations of vecuronium, acetylcholine release was increased, while at greater concentrations acetylcholine release was reduced [26]. This may indicate that vecuronium interacts with two distinct populations of presynaptic acetylcholine receptors [24] or that the *in situ* effects of cholinergic antagonists (or agonists) on neuromuscular transmission are mediated, in part, by the central nervous system [25]. Whether the interaction between vecuronium and betamethasone occurs at presynaptic cholinergic receptors has not been demonstrated in this

report, but it would be of interest to examine further the interaction at the neuromuscular junction between corticosteroids and other cholinergic agonists-antagonists in terms of pre- and postjunctional effects.

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REFERENCES

1. Meyers EF. Partial recovery from pancuronium neuromuscular blockade following hydrocortisone administration. *Anesthesiology* 1977; 46: 148-150.
2. Laffin MJ. Interaction of pancuronium and corticosteroids. *Anesthesiology* 1977; 47: 471-472.
3. Reddy P, Guzman A, Robalino J, Shevde K. Resistance to muscle relaxants in a patient receiving prolonged testosterone therapy. *Anesthesiology* 1989; 70: 871-873.
4. Parr SM, Galletly DC, Robinson BJ. Betamethasone induced resistance to vecuronium: a potential problem in neurosurgery? *Anaesthesia and Intensive Care* 1991; 19: 103-105.
5. Rees D. Consideration of the inorganic and organic composition of mammalian perfusion solutions. In: Doring MJ, Dehnert H, eds. *Isolated Perfused Organ Preparations*. March: Biomesstechnik-Verlag, 1989; 85-94.
6. Torda C, Wolff HG. Effect of adrenotrophic hormone of pituitary gland on ability of tissue to synthesize acetylcholine. *Proceedings of the Society for Experimental Biology and Medicine* 1944; 57: 137-139.
7. Torda C, Wolff HG. Effects of hypophysectomy and adrenocorticotrophic hormone on neuromuscular function and acetylcholine synthesis. *American Journal of Physiology* 1950; 161: 534-539.
8. Arts WF, Oosterhuis HJ. Effect of prednisolone on neuromuscular blocking in mice *in vivo*. *Neurology* 1975; 25: 1088-1090.
9. Leeuwijn RS, Veldsema-Currie RD, Van Wilenburgh H, Ottenhof M. Effects of corticosteroids on neuromuscular blocking actions of d-tubocurarine. *European Journal of Pharmacology* 1981; 69: 165-173.
10. Webb SN, Parker SG. Effect of corticosteroids on partially curarised skeletal muscle. *International Congress of Pharmacology* 1978; 7: 477.
11. Riker WF, Hall ED, Baker T. Glucocorticoid unmasking of an anti-curare action of curare. *Pharmacologist* 1977; 19: 197.
12. Hall ED. Glucocorticoid modification of the responsiveness of a fast (type 2) neuromuscular system to edrophonium and d-tubocurarine. *Experimental Neurology* 1980; 69: 349-358.
13. Hall ED. Glucocorticoid effects on the electrical properties of spinal motor neurons. *Brain Research* 1982; 240: 109-116.
14. Wolters EChMJ, Leeuwijn RS. Effects of corticosteroids on the phrenic nerve-diaphragm preparation treated with hemicholinium-3. *Neurology* 1976; 26: 574-578.
15. Veldsema-Currie RD, Wolters EChMJ, Leeuwijn RS.

- The effect of corticosteroids and hemicholinium-3 on choline uptake and incorporation into acetylcholine in rat diaphragm. *European Journal of Pharmacology* 1976; 35: 399-402.
16. Van Wilenburg H, Njio KD, Belling GAC, Van Den Hoven S. Effects of corticosteroids on the myoneural junction. A morphometric and electrophysiological study. *European Journal of Pharmacology* 1982; 84: 129-137.
 17. Van Wilenburg H. The effect of prednisolone on neuromuscular transmission in the rat diaphragm. *European Journal of Pharmacology* 1979; 55: 355-361.
 18. Veldsema-Currie RD, Van Wilenburg H, Labruyere WTh, Langemeijer MWE. Presynaptic, facilitatory effects of the corticosteroid dexamethasone in rat diaphragm: modulation by beta-bungarotoxin. *Brain Research* 1984; 294: 315-325.
 19. Dalkara T, Onur R. Facilitatory effects of dexamethasone on neuromuscular transmission. *Experimental Neurology* 1987; 95: 116-125.
 20. Dreyer F, Peper K, Sterz R, Bradley RJ, Muller KD. Drug-receptor interaction at the frog neuromuscular junction. *Progress in Brain Research* 1979; 49: 213-223.
 21. Wilson RW, Ward MD, Johns TR. Corticosteroids: A direct effect at the neuromuscular junction. *Neurology* 1974; 24: 1091-1095.
 22. Hofmann WW. Antimyasthenic action of corticosteroids. *Archives of Neurology* 1977; 34: 356-360.
 23. Torda TA, Kiloh N. Myoneural actions of Org NC 45. *British Journal of Anaesthesia* 1982; 54: 1217-1221.
 24. Starke K, Gothert M, Kilbinger H. Modulation of neurotransmitter release by presynaptic autoreceptors. *Physiological Reviews* 1989; 69: 864-989.
 25. Haggblad J, Heilbronn. Release of acetylcholine at the endplate of the rat—evidence against a muscarinic acetylcholine autoreceptor. *British Journal of Pharmacology* 1983; 80: 471-476.
 26. Baker T, Aguero A, Stance A, Lowndes HE. Prejunctional effects of vecuronium in the cat. *Anesthesiology* 1986; 65: 480-484.

THE PRONE POSITION FOR THE SURGICAL PATIENT: A HISTORICAL REVIEW OF THE PRINCIPLES AND HAZARDS†

J. M. ANDERTON

Surgery on the spinal axis

Surgery for the correction of gross spinal abnormality or for the management of intradural pathology remains relatively rare and this work is performed in a few specialized centres. However, lumbar disc surgery is now extremely common and is performed in all neurosurgical units and in most hospitals with an orthopaedic department. Before 1934, occasional cases of prolapsed intervertebral disc had been described in the literature; usually they had been misdiagnosed and treated as extradural chondromas. Goldthwait [14] in 1911 proposed that disc prolapse could be a cause of compression of the cauda equina producing symptoms of sciatica and low back pain. Sporadic clinical case reports appeared thereafter and important confirmatory pathological observations were also made about this time [54]. In 1934, the neurosurgeon William J. Mixter and the orthopaedic surgeon Joseph S. Barr wrote a paper establishing the degenerative aetiology of disc herniation and its relation to sciatic pain [31]. Their work is regarded as the "classic" in this field. It was read at a meeting of the New England Surgical Society on September 30, 1933 at Boston and published in the *New England Journal of Medicine*.

Early accounts of lumbar intervertebral disc surgery

The first article mentioning any aspect of anaesthesia for lumbar disc surgery was by Love and Camp of the Mayo Clinic [27]. An ether anaesthetic administered by open drop method over the end of a Magill tracheal tube was used. Cervical laminectomies were performed with the

patient in the upright position; other laminectomies were performed with the patient prone. In the latter, the torso was supported by two rolled pillows placed in the longitudinal axis so as not to interfere with ventilation. Surgery in the lower lumbar region was facilitated by placing a large soft pillow between the symphysis pubis and xyphoid process in order to increase the prominence of the lumbar spinous processes.

Between 1944 and 1956, several authors refer to laminectomy performed with the patient positioned on a "special operating table" [32, 41, 48]. However, it is likely that these were available only in the few neurosurgical centres where surgeons were already accustomed to open the spinal canal. Even up to 1950, this was a relatively rare event; Hunter [21], writing at that time stated that he had been unable to find a single reference in the literature to anaesthesia for spinal tumours. Haemorrhage was a constant problem, so much so that Pearce [36] stated that many workers in this field chose to operate with the patient in the lateral position so that the blood could run out of the wound rather than collect in the depths of the cavity. Bonica and Lyter [5] found that blood loss during operations on the spinal column varied from 658 to 992 ml.

Problems of positioning were compounded further by the limitations of the current general anaesthetics administered without the benefit of neuromuscular blocking drugs. The surgeon was faced, therefore, with access made difficult by

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KEY WORDS

Complications: positional. History. Position: prone position.

spasm of the overlying erector spinae muscles, compounded by any anterior spinal curvature opposing the edges of the vertebral bodies through which degenerated disc material needed to be extracted. Anaesthetic and position-related venous back pressure producing excessive haemorrhage added further insult to injury. The problem of "undoing the anterior lumbar curve" alluded to previously by Love and Camp [27] must have been of considerable significance and was mentioned by two further writers: Hunter [21] stated that it was not uncommon for the surgeon to request that the patient be positioned prone over a transversely placed metal bar, and Lipton [26] stated that the surgeon would want "the table split and the abdomen packed with pillows". Whichever method was used, the aorta and inferior vena cava must have been occluded partly or completely, with congestion and haemorrhage. Communication between the inferior vena cava and the extradural veins via the lumbar plexus was already well documented [4, 7, 35].

The first European article relating to anaesthesia for lumbar disc surgery was published in 1942 by Wiberg [52]. Dr Love, surgeon to the Mayo Clinic, had visited the Karolinska clinic in Sweden in 1939. Wiberg commented that they started by using an infiltration local anaesthetic technique advocated in the U.S., but later modified it by addition of either general anaesthesia or intrathecal local anaesthetic. This was necessitated by the excruciating pain experienced by patients when inflamed and stretched spinal roots were touched. Unfortunately, he did not mention positioning the patient for surgery. In the U.S.A., Smith, Deery and Hagman [41], describing 100 cases of surgery for herniation of the nucleus pulposus operated on between 1937 and 1943, stated that "the operation was done on a special table which places the patient in the kneeling position with the hips flexed at 90°" and he considered this positioning "an important point in the technique". Nitikman [34] in 1946, describing a spinal (intrathecal) anaesthetic technique, also mentioned the use of a special table with a "gatch" which was raised acutely at the level of the crest of the ilium. The patient was placed over this and then two pads, 20 cm wide and 7.5 cm thick, were placed from iliac crests to the xiphoid process; these pads were tapered to half their thickness to support the chest. Similar methods using only lateral bolsters [21] or specially shaped foam pads [3] have also been

described. Loss of shape and support occurs with repeated use and contamination with blood and cleaning fluids may be a risk to other patients and staff.

Falconer, McGeorge and Begg [12], reviewing 100 cases in 1948, briefly mentioned that patients were positioned with a sandbag under the groins and a pillow beneath the chest. They also pointed out that positioning the patient so that the lumbar spine was hyperextended was a useful test of the macroscopically "normal" but degenerate disc. With hyperextension, it bulges posteriorly into the vertebral canal, whereas the normal one does not.

Over-enthusiastic surgical attempts to clear the entire intervertebral disc space may result in perforation of anterior intervertebral ligaments and damage to the underlying major blood vessels. The first reports of this complication occurred as early as 1945 [25]. Fortunately, the damage on that occasion was not acute and resulted in an arteriovenous fistula between the right common iliac artery and the inferior vena cava. It was discovered some 7 months after the initial laminectomy and was repaired successfully. In 1948, Holischer [19] described a similar case, although major vessel damage was suspected at the time of discectomy. By 1954 Harbison [16], also after experience of a similar case, conducted a survey of 100 surgeons in the U.S.A. and obtained reliable information on another 25 injuries to major blood vessels occurring as a result of surgery for intervertebral lumbar disc protrusion. There was a 61% mortality from this complication in the series; six of the patients who survived developed arteriovenous fistulae and one subsequently died. Of great importance was the finding that in more than 50% of patients such injuries do not manifest themselves by external haemorrhage at the surgical site, and unless both the anaesthetist and surgeon are aware of this possibility, unexplained hypotension may be ascribed to other causes. Methods of prone positioning currently in use at that time, which forced the great vessels against the lumbar interspaces, were suggested as a contributory factor in the aetiology of this complication. In the same year, Seeley, Hughes and Jahnke [39] reported a further two cases. They examined vessels likely to be damaged at different intervertebral disc levels and urged that immediate transabdominal exploration and repair should be carried out when this complication is confirmed or seriously suspected.

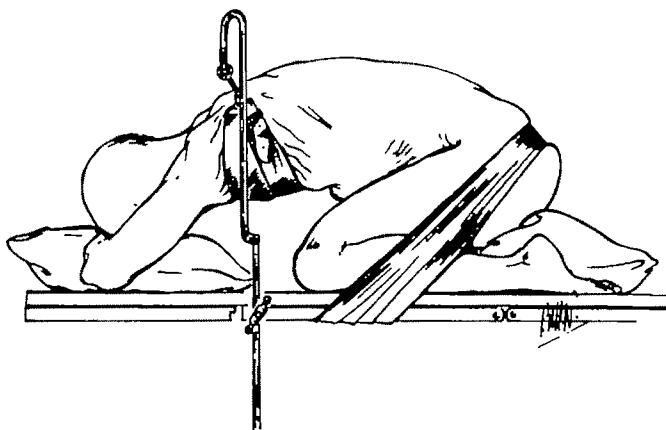


FIG. 1. The kneeling position as described by Ecker (1949 [10]).



FIG. 2. The Mohammedan Prayer position as described by Lipton (1950 [26]).

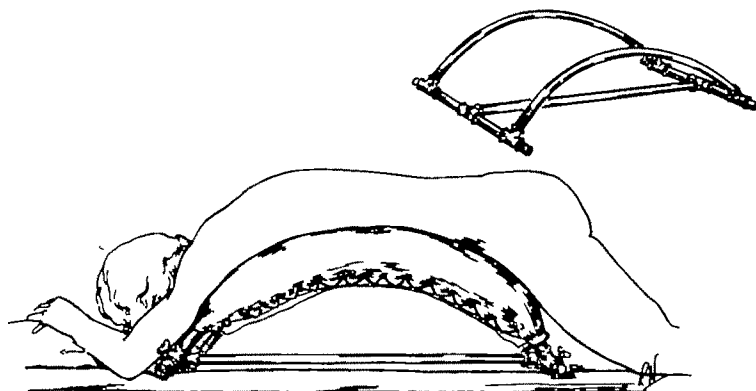


FIG. 3. The first description of a "Frame" for supporting the prone patient (Moore and Edmonds, 1950 [32]).

Harbison's survey [16] also revealed one case of injury to the small bowel. This was recognized at the time of operation by the appearance of intestinal mucosa in the jaws of the pituitary rongeur. Immediate laparotomy was performed with closure of the torn bowel, with good results. A similar case reported by Smith and Estridge [42] was not diagnosed conclusively until laparotomy on the second day after operation. Damage to the bowel is, however, quite rare; only

three of 140 reported intra-abdominal injuries were in this category.

Keeping external pressure away from the anterior abdominal wall

In an attempt to overcome the adverse effects of external pressure on the anterior wall, Ecker [10] in 1949 (fig. 1) and Lipton in 1950 [26] (fig. 2) described similar positions. The thighs were well flexed but splayed out away from the abdominal

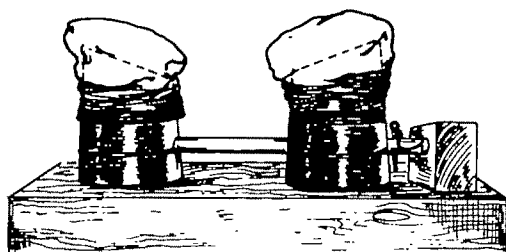


FIG. 4. Pelvic support made from bed blocks. The right limb is movable on the metal bar and fixed by split-pins (Taylor, Gleadhill and Bilsand, 1956 [48]).

wall. The chest was supported either by a sling (Ecker) or pillows (Lipton). However, in 1952 Gordon and Newman reported a death from acute renal failure as a result of crush injury to thigh and calf muscles [15]. A similar but non-fatal case was reported in 1969 by Keim and Weinstein [22].

By 1950 it had become apparent to Moore and Edmunds [32] that the shortcomings of specially adapted tables and the less sophisticated techniques of simple propping with sandbags and pillows required further development. They published their experience of using a "frame" over which the patient could be positioned (fig. 3). It had the twin advantages of easy storage, transport and use, together with minimal physiological disturbance for the patient. Both the Mackay [29] and the Wilson "frames" were of similar design, but with greater facility for adjustment.

Specific support for the pelvis

The next important advance was an article published in 1956 in *British Journal of Anaesthesia* by Taylor, Gleadhill and Bilsand [48], emphasizing the need to minimize extradural venous bleeding by avoiding abdominal and thoracic compression. This was achieved by an easily made adjustable prop which could be used on any conventional operating table. The authors

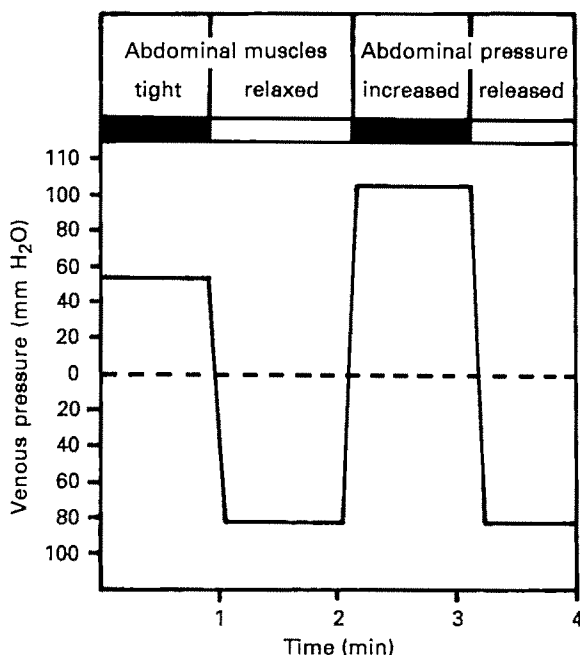


FIG. 6. Measurements of the inferior vena cava pressure in the prone position made by Pearce in 1957 [36].

acknowledged that the principle involved was copied from an operating table designed specially by Professor Norman Dott of Edinburgh. This table had a series of vertically adjustable U-shaped segments arranged across it. The patient was placed prone, and then the segment at the level of the iliac crests was raised well above the others, allowing the abdomen to sink in front of it. He postulated that, as pressure in any valveless venous system was least at its highest point, the body should be placed on the table so that the operation field is at the highest point. The thorax was supported also, but the abdomen and neck were free of external pressure. The prop (figs 4, 5) has one fixed support, and one free to be adjusted

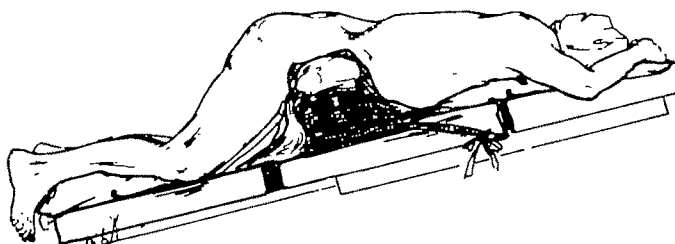


FIG. 5. Lateral view showing the abdomen lifted clear of the table with the weight distributed between the pelvis, legs and shoulders.

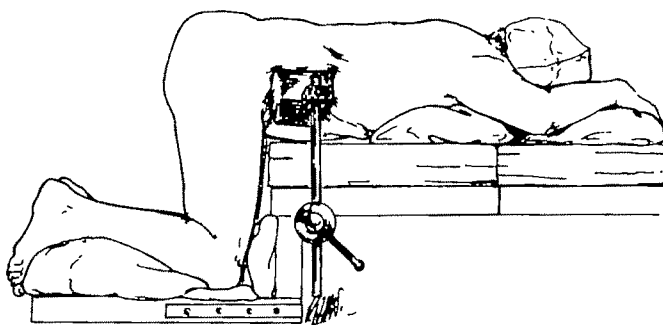


FIG. 7. The Georgia Prone Position (Smith, Gramling and Volpitto, 1961 [45]).

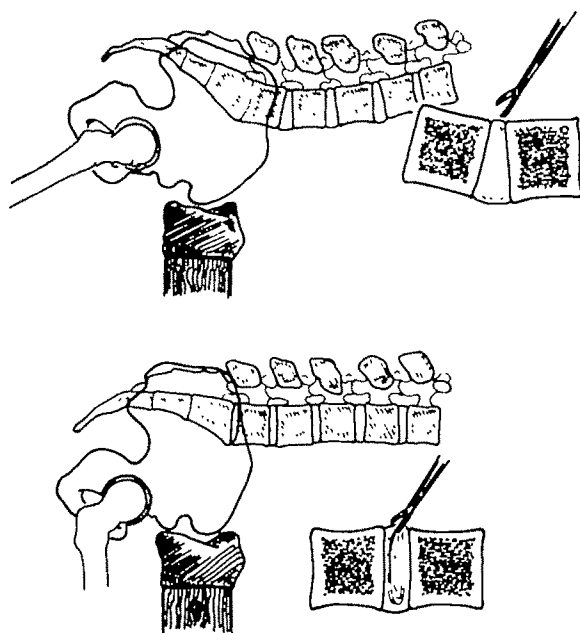


FIG. 8. X-ray studies demonstrate well that femoral flexion can abolish the lumbar curve and improve posterior access to the intervertebral space.

according to the width of the patient's pelvis. The original description shows the lateral rim of both supports higher than the medial margin, to prevent the patient slipping sideways. This is an extremely important precaution and it is a pity it was not incorporated into other copies of this prop, for example the Manchester version. Without such a precaution, any displacement of the patient always leads to compression of one femoral-neurovascular bundle in the groin and operating conditions are impaired. (This is also a risk with other propping systems in which the individual

props are not fixed to a firm base plate.) Scientific support for the concepts outlined above came quickly on the heels of this publication. Pearce [36], in a "Registrar's Prize" paper to the Anaesthetic Section of the Royal Society of Medicine in 1957, provided the first recordings of inferior vena cava pressures made with a patient in the prone position (fig. 6). From a diagram of the positioning of his patients, it was clear that the "built-up" sides of the blocks prevented lateral displacement.

A modified operating table

Smith, Gramling and Volpitto [45] in 1961 described the "Georgia Prone Position" using fixed props beneath the pelvic crests. The thighs were flexed at right angles and some of the patient's weight was supported by the knees (fig. 7). Drawings from lateral x-rays taken in this position show the effect on spinal curvature of lowering the thighs to rotate the pelvis backwards and downwards. The lumbar spine becomes flatter and this can be advantageous to the surgeon by improving posterior access to the intervertebral disc space (fig. 8). Their subjective tests of conscious volunteers placed in the prone position showed that the patient's back and neck must be in the same plane to allow the head to be turned painlessly to each side; the arms should rest on the operating table "above" the head to prevent discomfort; the infraclavicular fossae should be free of pressure points and, in female patients, the breasts must be displaced laterally. Transverse rolls placed anywhere under the body (except under the ankles), produce pain, particularly if under the chest, iliac spine, pubis or trochanters. Later (1964) Smith [43] described a special device for use in this position, based on an adjustable automobile jack which could be placed below the

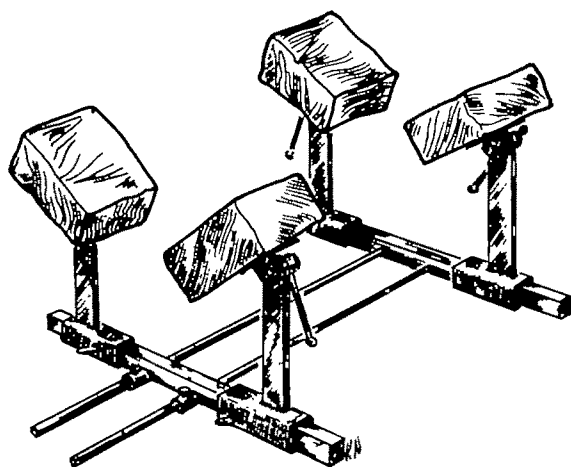


Fig. 9. The Relton and Hall Frame designed for spinal fusion surgery using the Harrington Rod.

knees both for support, and for accurate positioning, in order to produce the desired degree of spinal curvature. By 1974, however, Smith [44] appeared to have abandoned the Georgia prone position in favour of adjustable props similar in principle to the technique of Taylor and Pearce.

Influence of reconstructive spinal surgery

The need to provide a satisfactory support system for patients undergoing orthopaedic surgery for kyphoscoliosis correction became necessary in the 1960s. Their deformity made initial positioning difficult and potentially unstable, and this was compounded when further loss of skeletal support occurred during operation. Operative blood loss was measured in a series of 44 patients by Relton and Conn [37]. Seventy-five percent of the patients lost more than 50% of their circulating blood volume. Following these studies, Relton and Hall [38] published their description of an "operation frame for spinal fusion". This was the first, and only, frame in which four individual, adjustable supports were arranged on a rail system, allowing accurate positioning irrespective of skeletal deformity (fig. 9). Blood loss in the initial series of patients studied compared favourably with that of Relton and Conn. When the supports are positioned anterolaterally, they tend to facilitate correction of the scoliosis; any tendency towards hyperextension of the vertebral column may be counteracted partially by lowering the legs (as first demonstrated by Smith). Relton and Hall did not recommend use of the frame for laminectomy for

lumbar disc protrusion because of the lordosis it induced. However, it is possible to use the lower pelvic supports mounted on a different base plate for this purpose (fig. 10) (in the same manner as Taylor's prop) provided that some flexion of the thighs is obtained. The chest is then supported on pillows or a foam pad. The full frame has been advocated by Humphries and colleagues [20] for use in neurosurgical procedures on the upper cervical spine and posterior fossa in children. Mouradian and Simmons [33] have described a method of combining the Foster or Stryker frame with the Relton and Hall frame so that continuous skeletal traction may still be applied whilst the patient is undergoing surgery.

The acute neurological complications arising as a result of corrective surgery for scoliosis were reviewed in 1975 by MacEwan, Bunnell and Krishnaswami [28]. Seventy-four major complications involving the spinal cord occurred in 7885 operations, 50% complete paraplegia and 50% partial paraplegia. Only 36% recovered completely.

The "seated" prone position

Probably the most significant advance in prone positioning was made by Tarlov [46] in 1967 when he published a description of support via the ischial tuberosities—that is, a seated prone position with the operating table tipped steeply to approximately 45° (fig. 11). It is interesting that Ecker [10], Lipton [26] and Smith, Gramling and Volpito [45] came close to this position without seeing that final development. Taylor, Gleadhill and Bilsand [48] did describe the use of a bicycle saddle to provide further support for their iliac crest propped position, but again failed to see the advantages of using it as a primary method. Other authors publishing later descriptions of the same idea include Hastings [17], Laurin and colleagues [23] and Dinmore [8]. The chest pad or pillows should not encroach on the neck or compress the epigastrium. There is no pressure on either the viscera or inferior vena cava, and vessels in the groin are not at risk, as they are in many other methods of support.

Even in procedures of very long duration, it is rare to see any adverse effects from pressure on the knees. Postoperative phlebotrombotic problems in the lower limbs are also rare. Tarlov [47] described two minor cases in 300 operations, and ascribed these to excessive flexion of the hips and knees. External compression apparatus can be

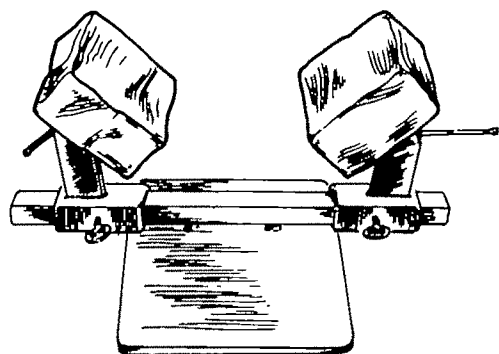


FIG. 10. Props from the "Relton and Hall" frame with a special base plate may be used for pelvic support in surgery of the lumbar spine.

applied routinely below the knees. In 1969, Laurin and colleagues measured inferior vena cava pressure and found it to be as little as 2 cm H₂O [23]. Venograms of the inferior vena cava were compared with the patient on a conventional laminectomy frame and on the Tarlov seat. With the latter, back flow up into the extradural veins did not occur and more rapid emptying into the right atrium of the heart was evident.

The illustration in Tarlov's original article and in a later one [47] shows the patient's back to be more or less horizontal. Hastings [17] and Dinmore [8] both specify this in their text. Laurin and colleagues [23] advised that the chest should be slightly lower than the buttocks, to favour drainage of the vena cava into the left atrium. However, taking the weight off the ischial tuberosities may make the patient less stable, and

TABLE I. *Effects of position on central venous pressure and airway pressure in laminectomy patients* [6]

Patient weight (lb)	Operation	Central venous pressure (cm H ₂ O)		
		Supine under general	Prone on laminectomy frame	Sitting prone position
200	Thoracic	1	14	1
110	Lumbar	3	10	2
150	Thoracic	10	16	2
200	Lumbar	5-6	8-10	1
170	Thoracic	3-4	12-14	1-0
250	Lumbar	1	16	1
175	Lumbar	2	13	0
150	Lumbar	6	7.5	0
200	Lumbar	4	6	0
180	Lumbar	6-7	10-12	1-0
170	Lumbar	4	8	0
180	Lumbar	3-4	8	0

it must be remembered that, in any situation where veins are opened inadvertently at a surgical procedure taking place above heart level, there is theoretically a risk of venous air embolism. Clearly this should not occur when the central venous pressure is greater than the vertical distance between the atrium and the open veins. However, with the "Tarlov" position central venous pressure is usually small—approximately 0-2 cm H₂O with the back horizontal. This was confirmed by Cook and colleagues [6] in 12 patients (table I). Distephano and colleagues [9] gave a comparison of inferior vena cava pressures measured during surgery for lumbar procedures and again confirmed that the Tarlov position is superior in this

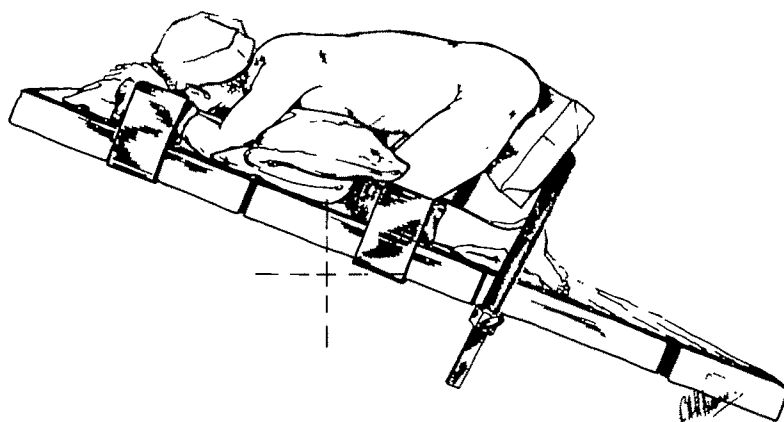


FIG. 11. Tarlov (1967 [46]) described this as the "knee chest position". However, the use of the term "seated prone" distinguishes it from similar less satisfactory versions (*vide* Lipton [26] and Ecker [10]).

TABLE II. Central venous pressure values in a variety of positions [9]

Arrangement	Average CVP (cm H ₂ O)
Georgia prone	20.7
Prone chest rolls	15.9
Lateral decubitus	11.1
Wilson frame	10.1
Tuck position	9.4
Hastings frame	1.4

respect (table II). However, the actual risk of venous air embolism seems to be very small indeed. There is one report of a fatality in the literature [40] but in this patient posterior fossa surgery was being performed for a large arterio-venous malformation.

The question of whether or not patients should have a central venous pressure catheter sited in the right atrium was raised by Goldberg [13] in 1977. Tarlov [47] stated that in his experience of several hundred patients, it was not necessary for lumbar surgery. He made the point that the spinal veins, unlike the large intracranial veins and dural sinuses, are not kept open by bony and fascial attachments and this may be the reason for the apparent safety of the position despite known small central venous pressures. In further correspondence on the subject Albin and colleagues [1] advocated the use of both right atrial catheters and Doppler ultrasonic transducers, even for lumbar surgery, and quoted detection of venous air embolism in neurosurgical patients in the lateral, supine and prone positions with gradients between the wound and the heart as small as 5 cm. It would appear from more recent work by Backofen and Schauble [2] that the value of a right atrial catheter lies more in its propensity as a route

of aspiration than for the information it may provide. They recommend that poor risk patients who would be unlikely to tolerate a reduction in cardiac index of around 20% should have arterial and thermodilution catheters inserted.

A 15-year survey was undertaken by Wayne [50] in 1984 and he reported favourably on the use of this position. In 253 patients, there was only one case of deep vein thrombosis in the leg with uncomplicated pulmonary embolus. Together with Tarlov's experience, this represents a fairly impressive safety record. Serious air embolism is a very rare event when the position is used for lumbar surgery.

A different approach—the evacuable mattress

The late Dr J. V. I. Young of the London Hospital first drew attention to the use of an "evacuatable" mattress (Evac M) (fig. 12) in 1982 and published an account of its more general applications [55]. This method of support spreads the load evenly over the entire anterior body surface, thus minimizing pressure sequelae. Soft plastic granules are enclosed in a heavy duty, airtight flexible plastic container. Air may be sucked out or let in through a stoppered valve, causing a change in consistency, so that it holds its shape until opened to the atmosphere again. The anaesthetized patient is turned into the prone position whilst the mattress is still soft; the mattress is then moulded to fit the body contours, ensuring a slight gap beneath the epigastrium, and air is sucked out. The excellent heat retaining properties are a useful advantage.

Specific support for the head and neck, and protection for the face

Patients with symptoms of neck pain are often anxious before operation that their disability be

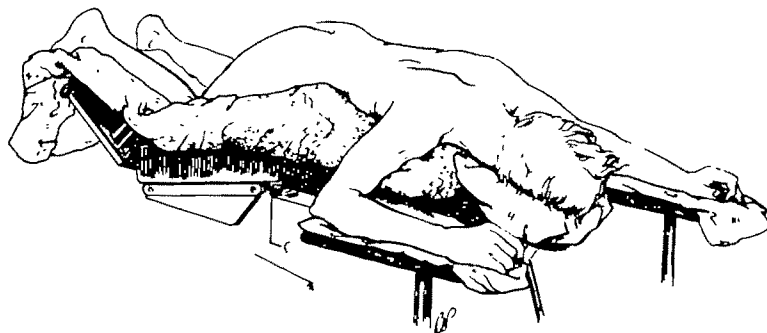


FIG. 12. Prone position using the evacuable mattress.

noted, for fear that it will be worse afterwards. Both cervical hyperextension and rotation must be avoided. Younger patients with capacious cervical spinal canal are probably not at much risk from hyperextension, but the older patient with a canal narrowed by osteophytes may develop compromised spinal cord blood supply if the canal is narrowed further by bad positioning. Ehni [11] and Wilkes [53] reported cases of postoperative neurological deficit as a result of supine, lateral and lithotomy positioning and, although there do not appear to be any similar reports associated with the prone position, it is reasonable to assume that the cervical spinal canal may also be compromised. Great care must therefore be taken both in the actual turning process, when a short but severe episode of hyperextension can very easily take place and in the final resting position. Of the latter, Young [55] states "that it is not often appreciated how much higher the shoulders have to be than the head in the face down position to avoid extending the neck, a good guide is the absence of a transverse skin crease at the back of the neck". Flexion of the neck and the atlanto-occipital joint should be avoided in patients with posterior fossa tumours as it may provoke brainstem ischaemia. It may be difficult to diagnose this without the use of somatosensory evoked potential monitoring [30].

Damage to the eyes in a patient in the prone position is a serious complication. The first report in the literature [49] described two cases of retinal ischaemia with unilateral blindness occurring during pulmonary resection carried out in the prone position. A rubber cushioned horse-shoe support was used. In each case undetected rotation of the head occurred and protracted direct pressure on the globe ensued. In 1954, eight similar cases were reported from the Mayo Clinic; all had rested on the horse-shoe in either the prone or sitting position [18]. Experimental work on monkeys by the same authors suggested that orbital pressure, blood loss and induced hypotension were required to reproduce the same syndrome as that observed in man. A further case of unilateral blindness occurring after the prone position was presented at a Neurosurgical Anaesthetists' meeting in 1989 [Cooper and Ingham, personal communication]; again the horse-shoe headrest was implicated. It would appear that there is no justification nowadays to use the horse-shoe headrest when surgery is being performed in the lumbar or thoracic spinal

regions. All that is necessary is a pillow or foam rubber support placed so that the weight of the head is taken directly by the forehead and there is a clear gap beneath the eyes and the top of the nose. The patient's head should be in the neutral position, without rotation of the neck [45].

For surgery to be carried out on the neck or posterior cranial fossae, the horse-shoe remains an option for head support. However, it would be wise to ensure as far as possible that the head is strapped securely to the support and if minor adjustments are required subsequently, both the horse-shoe and the head should be moved together. The eyes should be covered to protect them from drying, abrasion or fluid contamination. Patients with intraocular lens implants are at risk of haemorrhage or secondary damage to the posterior surface of the cornea should external pressure on the eyeball cause the lens to become displaced.

A further problem with the use of the horse-shoe headrest is damage to the skin over the malar areas. Blistering and even full thickness skin loss may result from excessive pressure, abrasive forces, or both. Craniotomy involving the use of the Gigli saw is a particular risk, as the reciprocating movement inevitably rubs the malar skin against the headrest.

Alternatively, the Mayfield neurosurgical skull clamp may be used. There do not appear to be any reports of untoward effects related to the eyes, but there is always the potential for a pin to slip or become displaced.

Finally, it is worth noting that, should blindness ensue unexpectedly and for no obvious external reason, an embolic episode affecting the retinal artery should be considered. Fat, particularly, has been implicated and paradoxical air embolism is a more rare possibility.

A new hazard of prone positioning

Weinlander, Coombs and Plume [51] reported a patient who, having previously had coronary artery bypass surgery, showed ECG evidence of adverse effects on myocardial blood flow when anaesthetized and placed in the prone position. ECG abnormalities noted during surgery were confirmed in the recovery room to represent massive anterolateral ischaemia. Emergency coronary revascularization was proceeded to and at operation both saphenous vein bypass grafts were found to be patent and pulsatile. A further graft was inserted and a good recovery obtained. It would appear that the thin-walled veins used as

coronary grafts easily became compressed by pressure on the anterior chest wall. This mechanical cause of graft obstruction is reversible. Full 12-lead intraoperative ECG monitoring is now technically possible and should be considered in such patients. It would be unwise to allow surgery to begin until adverse effects of positioning can be confidently excluded.

CONCLUSIONS

The quest for the most satisfactory method of prone positioning has been influenced by the necessity of providing good operating conditions with minimal haemorrhage and by the reporting of complications and hazards encountered. Some very serious complications have been reported and they can be classified under three headings.

First, there are those arising directly *as a result of the method of prone positioning*. The more serious of these include crush injuries to limb muscle resulting in anuria; excessive extradural venous haemorrhage from back pressure in the femoral veins or abdomen; pressure necrosis of skin, neuropraxia and blindness.

The second group of complications arise *as a consequence of the surgery being performed*. Damage to underlying major vessels or even perforation of the bowel are well recorded and represent dangerous risks of intervertebral disc surgery. Extensive haemorrhage and spinal cord damage may occur with reconstructive spinal surgery. Venous air embolism is possible when the operating site is above the level of the patient's right atrium.

Finally, there are the *complications associated with anaesthesia* in the prone position. The technical hazards are probably greater than the physiological ones, although in the very obese or poor risk patient the latter cannot be dismissed. The cornerstone of anaesthetic technique is the correct placement and security of a non-kinking tracheal tube. Oral secretions gravitating from the mouth may loosen the retaining strapping; inadvertent endobronchial intubation may be produced by the inevitable changes of head position associated with the turning procedure. Special attention should be taken to avoid hyperextension of the patient's neck. Lee, Barnes and Nagel [24] were so concerned with the actual hazards of the turning procedure that they devised a method of "awake pronation" under neuroleptanalgesia.

Whichever method of prone positioning is chosen, it is wise always to check the peripheral

arterial pulses in the feet before finally draping the patient, and the use of external compression apparatus to the legs may help to prevent venous stasis. The advent of modern monitoring techniques, particularly Sp_{O_2} , FE_{CO_2} , and reliable non-invasive arterial pressure devices certainly help to provide early warning of both surgical and anaesthetically related problems. If it is necessary to use one of the older or less stable methods of positioning, any adverse cardiovascular effect arising in the course of the operation should alert the anaesthetist to checking the patient's position. Serious and otherwise unexplained hypotension should be managed by immediately abandoning the operation and returning the patient to the supine position.

The Tarlov seated position with the table tipped to 45° and the back horizontal appears to be the most satisfactory for all types of lumbar disc surgery and for some operations at higher levels. It is extremely stable, applicable to a wide range of body size and shape, and is the least likely to result in venous back pressure at the operating site. It appears to have an excellent safety record.

SUMMARY

Since the 1940s there has been an increase in the number of patients submitted for surgery of the spinal axis necessitating use of the prone position. Specifically designed operating tables were both rare and expensive, and probably only existed in a few highly specialized centres. Apparatus which could be easily made locally and used in conjunction with normal operating tables has been invented and generally used to good effect. The important historical landmarks in these developments are traced and a review of the methods and hazards is presented. Similar methods evolved almost simultaneously in differing centres. It is recommended that the Tarlov "seated prone" position should be widely used, in view of its physiological advantages and lack of adverse reports.

REFERENCES

1. Albin MS, Newfield P, Paulter S, Tung AL, Maivald P. Atrial catheter and lumbar disc surgery. *Journal of the American Medical Association* 1978; 239: 496.
2. Backofen JE, Schauble JF. Hemodynamic changes with prone position during general anesthesia. *Anesthesia and Analgesia* 1985; 64: 194.
3. Bardeen A. Special pad for patients in the prone position. *Anesthesiology* 1955; 16: 464-466.

4. Batson OV. The function of the vertebral veins and their role in the spread of metastases. *Annals of Surgery* 1940; 112: 139-149.
5. Bonica JJ, Lyter CS. Blood loss during surgical operations. *Anesthesiology* 1951; 12: 90-99.
6. Cook AW, Siddiqi TS, Nidzgorski R, Clark HA. Sitting prone position for the posterior surgical approach to the spine and posterior fossa. *Neurosurgery* 1982; 10: 232-235.
7. Cruveiller. Spine venous plexus communications. *Anatomie Descriptive* 1834; 3: 328.
8. Dinmore P. A new operating position for posterior spinal surgery. *Anaesthesia* 1977; 32: 377-380.
9. Distephano VJ, Klein KS, Nixon JE, Andrews TE. Intraoperative analysis of position and body habitus on surgery of the low back. *Clinical Orthopaedics and Related Research* 1974; 99: 51-56.
10. Ecker A. Kneeling position for operations on the lumbar spine. Especially for protruded intervertebral disc. *Surgery* 1949; 25: 112.
11. Ehni G. Significance of the small lumbar spinal canal. Cauda equina compression syndromes due to spondylosis. Part 4 Acute compression artificially induced during operation. *Journal of Neurosurgery* 1969; 31: 507-512.
12. Falconer MA, McGeorge M, Begg CA. Surgery of lumbar intervertebral disc protrusion. *British Journal of Surgery* 1948; 139: 225-249.
13. Goldberg D. Lumbar disc surgery in the knee-chest position: Preanaesthetic atrial catheter unnecessary. Questions and Answers. *Journal of the American Medical Association* 1977; 238: 253.
14. Goldthwait JE. The lumbo-sacral articulation. An explanation of many cases of "lumbago", "sciatica" and paraplegia. *Boston Medical and Surgical Journal* 1911; 164: 365-372.
15. Gordon BS, Newman W. Lower nephron syndrome following prolonged knee-chest position. *Journal of Bone and Joint Surgery. American Volume* 1952; 35A: 764-768.
16. Harbison SP. Major vascular complications of intervertebral disc surgery. *Annals of Surgery* 1948; 140: 342-348.
17. Hastings DE. A simple frame for operations on the lumbar spine. *Canadian Journal of Surgery* 1969; 12: 251-253.
18. Hollenhorst RW, Svien HJ, Benoit CF. Unilateral blindness occurring during anaesthesia for neurosurgical operations. *Archives of Ophthalmology* 1954; 52: 819-830.
19. Holscher EC. Vascular complications of disc surgery. *Journal of Bone and Joint Surgery* 1948; 30: 968-970.
20. Humphreys RP, Creighton RE, Hendrick EB, Hoffman HJ. Advantages of the prone position for neurosurgical procedures on the upper cervical spine and posterior cranial fossa in children. *Childs Brain* 1975; 1: 325-336.
21. Hunter AR. Anaesthesia for operations in the vertebral canal. *Anesthesiology* 1950; 12: 367-373.
22. Keim HA, Weinstein JD. Acute renal failure. A complication of spine fusion in the tuck position. *Journal of Bone and Joint Surgery. American Volume* 1970; 52A: 1248-1250.
23. Laurin CA, Migneault G, Brunet JL, Roy P. Knee-chest support for lumbosacral operations. *Canadian Journal of Surgery* 1969; 12: 225-250.
24. Lee C, Barnes A, Nagel EL. Neuroleptanalgesia for awake pronation of surgical patients. *Anesthesia and Analgesia* 1977; 56: 276-278.
25. Linton RR, White PD. Arterio-venous fistula between the right common iliac artery and the inferior vena cava; Report of a case of its occurrence following an operation for a ruptured intervertebral disc with cure by operation. *American Medical Association Archives of Surgery* 1945; 50: 6-13.
26. Lipton S. Anaesthesia in the surgery of retropulsed vertebral discs. *Anaesthesia* 1950; 5: 208-212.
27. Love JE, Camp JD. Root pain resulting from intraspinal protrusion of intervertebral discs. Diagnosis and treatment. *Journal of Bone and Joint Surgery* 1937; 19: 776-803.
28. MacEwan GD, Bunnell WP, Krishnaswami S. Acute neurological complications in the treatment of scoliosis. A report of the Scoliosis Research Society. *Journal of Bone and Joint Surgery. American Volume* 1975; 57: 404-408.
29. Mackay IM. A new frame for positioning patients for surgery of the back. *Canadian Anaesthetists Society Journal* 1956; 3: 279-282.
30. McPherson RW, Szymski J, Rogers MC. Somatosensory evoked potential changes in position-related brain stem ischemia. *Anesthesiology* 1984; 61: 88-90.
31. Mixer JM, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. *New England Journal of Medicine* 1934; 211: 210-214.
32. Moore DC, Edmonds LH. Prone position frame. *Surgery* 1950; 27: 276-279.
33. Mouradian WH, Simmons EH. A frame for spinal surgery to reduce intra-abdominal pressure while continuous traction is applied. *Journal of Bone and Joint Surgery* 1977; 59A: 1098-1099.
34. Nitikman G. Spinal anesthesia for operation on the vertebral column. *Anesthesia and Analgesia* 1946; 25: 52-57.
35. Norgore M. Clinical anatomy of the vertebral veins. *Surgery* 1945; 17: 606-615.
36. Pearce DJ. The role of posture in laminectomy. *Proceedings of the Royal Society of Medicine* 1957; 50: 109-112.
37. Relton JES, Conn AW. Anaesthesia for the surgical correction of scoliosis by the Harrington method in children. *Canadian Anaesthetists Society Journal* 1963; 10: 603-615.
38. Relton JES, Hall JE. An operation frame for spinal fusion. A new apparatus designed to reduce haemorrhage during operation. *Journal of Bone and Joint Surgery* 1967; 49B: 327-332.
39. Seely SF, Hughes CW, Jahnke EJ. Major vessel damage in lumbar disc operation. *Surgery* 1954; 35: 421-429.
40. Shenkin HN, Goldfeder P. Air embolism from exposure of posterior cranial fossa in prone position. *Journal of the American Medical Association* 1969; 210: 726.
41. Smith ADeF, Deery EM, Hagman GL. Herniation of the nucleus pulposus. A study of one hundred cases treated by operation. *Journal of Bone and Joint Surgery* 1944; 26: 821-828.
42. Smith RA, Estridge MN. Bowel perforation following lumbar disc surgery. *Journal of Bone and Joint Surgery* 1964; 46: 826-832.
43. Smith RH. A device for positioning the prone patient. *Anesthesiology* 1964; 25: 87-89.
44. Smith RH. One solution to the problem of the prone position for surgical procedures. *Anesthesia and Analgesia* 1974; 53: 221-224.
45. Smith RH, Gramling ZW, Volpito PP. Problems related

- to the prone position for surgical operations. *Anesthesiology* 1961; 22: 189-193.
46. Tarlov IM. The knee-chest position for lower spinal operations. *Journal of Bone and Joint Surgery* 1967; 49A: 1193-1194.
47. Tarlov IM. Lumbar disc surgery in knee-chest position. Preanaesthetic atrial catheter unnecessary. Questions and Answers. *Journal of the American Medical Association* 1977; 238: 253.
48. Taylor AR, Gleadhill CA, Bilsand WL. Posture and anaesthesia for spinal operations with special reference to intervertebral disc surgery. *British Journal of Anaesthesia* 1956; 28: 213-219.
49. Walkup HE, Murphy JD, Oteen NC. Retinal ischaemia with unilateral blindness—complications during pulmonary resection in prone position: Two cases. *Journal of Thoracic Surgery* 1952; 23: 174-175.
50. Wayne SJ. A modification of the tuck position for lumbar spine surgery. A 15-year follow up study. *Clinical Orthopaedics* 1984; 184: 212-216.
51. Weinlander CM, Coombs DW, Plume SK. Myocardial ischemia due to obstruction of an aortocoronary bypass graft by intraoperative positioning. *Anesthesia and Analgesia* 1985; 64: 933-936.
52. Wiberg G. Anaesthesia in operation for prolapse of an intervertebral disc. *Acta Chirurgica Scandinavica* 1942; 87: 380-384.
53. Wilkes LL. Paraplegia from operating position and spinal stenosis in non-spinal surgery. *Clinical Orthopaedics* 1980; 146: 148-149.
54. Wilkins RH. *Neurosurgical Classics*. New York and London: Johnson Reprint Corporation, 1965.
55. Young JVI, Anderton JM, Keen RI, Neave R. *Positioning the Surgical Patient*. London: Butterworths, 1988; 90.

EFFECTIVENESS OF PREOXYGENATION IN MORBIDLY OBESE PATIENTS

M. C. BERTHOUD, J. E. PEACOCK AND C. S. REILLY

SUMMARY

The time taken for the oxygen saturation (Sp_{O_2}) to decrease to 90% after preoxygenation was studied in six morbidly obese patients and six matched controls of normal weight. During apnoea the obese patients maintained $Sp_{O_2} > 90\%$ for 196 (SD 80) s (range 55–208 s), compared with 595 (SD 142) s (range 430–825 s) in the control group ($P < 0.001$). One patient in the obese group had desaturation before the onset of complete relaxation and tracheal intubation, without complications. Bedside lung function tests were not significantly different between groups and cannot be used as a predictor of the effectiveness of preoxygenation.

KEY WORDS

Anaesthetic techniques: preoxygenation. Complications: obesity.

Preoxygenation decreases the risk of hypoxia associated with induction of anaesthesia and intubation of the trachea. It is valuable also in patients whose respiratory or cardiac reserve is reduced, and when a delay in establishing a clear airway may be anticipated.

Patients with morbid obesity—that is, a body mass index (BMI) $> 35 \text{ kg m}^{-2}$ —have a greater risk of acid regurgitation and aspiration, a reduced respiratory and cardiac reserve and are associated with increased difficulty at tracheal intubation. It has been recommended that a rapid sequence induction of anaesthesia should be used for these patients [1]. We have examined the effectiveness of preoxygenation in morbidly obese patients.

Six morbidly obese patients (group 1) (mean weight 123.5 (SD 23.2) kg (range 104–153 kg) and BMI 49 (7.3) kg m^{-2} (range 42–58.4 kg m^{-2})), were matched for sex, age and height with six control subjects (group 2) (weight 63 (8.3) kg (range 52–76 kg) and BMI 23.1 (3.0) kg m^{-2} (range 18–26.3 kg m^{-2})). BMI and weight were significantly greater in the obese group (Student's *t* test, $P < 0.001$). Full preoperative assessment was performed on the ward on the day before surgery. One patient in each group was a smoker. All patients were assessed for difficulty in tracheal intubation using established scoring systems [2, 3]. No patient was excluded from the study because of anticipated difficulty. Forced vital capacity (FVC), forced expiratory volume in 1 min (FEV₁) and peak expiratory flow rate (PEFR), were performed before operation with the patient in the sitting and in the supine position.

Results are presented as percentage of predicted for height and age. FVC in group 1 was 85.0 (20.4)% (range 54–115%) in the sitting position and 85.3 (14.3)% (range 68–110%) supine; in group 2 it was 97.3 (8.9)% (range 87–110%) sitting and 96.0 (10.0)% (range 85–108%) supine. FEV₁ in group 1 was 97.5 (20.6)% (range 60–122%) sitting and 92.7 (17.1)% (range 63–116%) supine; in group 2 it was 103.0 (14.5)% (range 87–118%) sitting and 96.0 (10.0)% (range 84–109%) supine. PEFR in group 1 was 84.2 (16.4)% (range 59–104%) sitting and 78.8 (17.7)% (range 52–95%) supine; in group 2 it was 89.5 (16.5)% (range 65–105%) sitting and 89.8 (17.4)% (range 63–110%) supine. No statistical difference was found either between groups

METHODS AND RESULTS

After local Ethics Committee approval and written informed consent by the patients, we studied 12 patients undergoing elective abdominal sur-

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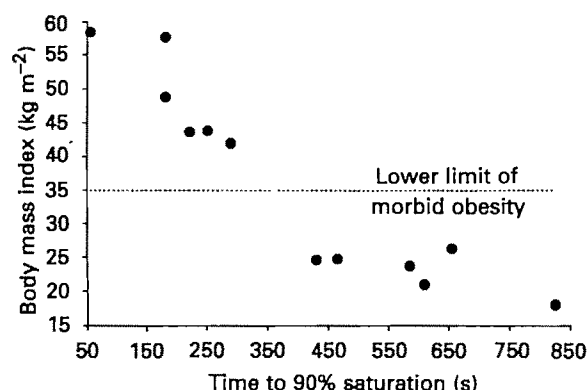


FIG. 1. Times to 90% saturation compared with BMI.

(Student's *t* test) or within groups between positions (paired *t* test).

Oral premedication consisted of ranitidine 150 mg the night before surgery and temazepam 20 mg with ranitidine 150 mg 1 h before induction of anaesthesia.

In the anaesthetic room, venous cannulation and, in the obese patients, left radial artery cannulation were performed under local anaesthesia. Monitoring consisted of arterial pressure measurement every 1 min throughout the period of study using a Dinamap or via the arterial cannula, continuous ECG, oxygen saturation (Sp_{O_2}) using the finger probe of a pulse oximeter (Kontron Instruments), and end-tidal carbon dioxide (E'_{CO_2}) (Kontron Capnograph).

Preoxygenation was performed using a fresh gas flow of 100% oxygen at 8 litre min^{-1} , from a flushed Mapleson A circuit, with an air-tight seal on the face mask. After 3 min of preoxygenation, anaesthesia was induced with propofol 10 mg ml^{-1} at a rate of 1200 ml h^{-1} , with cricoid pressure to minimize the risk of aspiration. On loss of verbal contact with the patient, alfentanil 0.01 mg kg^{-1} and suxamethonium 1 mg kg^{-1} (to a maximum of 100 mg) were given i.v. The patient's trachea was intubated and the tracheal cuff immediately inflated. The position of the tracheal tube was confirmed by seeing it pass between the cords, and by giving the patient a single breath of oxygen, in order to establish the presence of carbon dioxide in the expired gas. When the airway was secured, vecuronium 0.1 mg kg^{-1} (maximum 10 mg) was given to ensure apnoea. Anaesthesia was maintained by an infusion of propofol at 6 mg $\text{kg}^{-1} \text{h}^{-1}$. The tracheal tube was disconnected from the gas supply, and the patient

remained apnoeic until Sp_{O_2} decreased to 90%. The time from the injection of the suxamethonium, to this point was noted. The lungs were then ventilated with 100% oxygen. E'_{CO_2} at this point, and the time to recover to Sp_{O_2} 96% were noted. In the obese patients, arterial blood-gas tensions were measured before the onset of preoxygenation (Pa_{O_2} 11(1.9) kPa (range 8.6–13.4 kPa); Pa_{CO_2} 5 (0.6) kPa (range 4.1–5.6 kPa)), at tracheal intubation (Pa_{O_2} 42.9 (20.1) kPa (range 7.3–60.4 kPa); Pa_{CO_2} 5.8 (1.0) kPa (range 4.3–7.3 kPa)), and at Sp_{O_2} = 90% (Pa_{O_2} 7.9 (0.9) kPa (range 6.9–9.0 kPa); Pa_{CO_2} 6.2 (1.1) kPa (range 4.6–7.3 kPa)). The patient then proceeded to surgery.

Results for the time taken to desaturate to 90% and to resaturate to 96% after the start of IPPV were analysed using Student's *t* test. The mean time to 90% saturation was 196 (80) s (range 55–208 s) in the obese group and 595 (142) s (range 430–825 s) in the control group ($P < 0.001$) (fig. 1). The time to reach a saturation of 96% after the start of IPPV was 36.7 (13.3) s (range 25–45 s) in the obese group, and 22.5 (9.3) s (range 10–35 s) in the controls ($P = 0.062$). In one patient, Sp_{O_2} decreased to 82%, but in no other was it less than 87%. In no patient was $E'_{CO_2} > 7.3\%$, and there were no arrhythmias or hypertension.

COMMENT

This study demonstrates that preoxygenation for 3 min in morbidly obese patients provided a significantly shorter period of adequate oxygenation than in patients of normal weight. This is in agreement with the findings of Jense and colleagues [4]. One of our patients (BMI 58.4 kg m^{-2}) clearly demonstrated the increased risk associated with induction and tracheal intubation in this group, desaturating to 90% only 55 s after administration of suxamethonium, and before complete onset of relaxation. This patient's trachea was intubated, at first attempt, 65 s after the injection of suxamethonium, by which time Sp_{O_2} was 82%.

Bedside lung function tests with the patient in either the sitting or the supine position were not significantly different between groups. Preoxygenation is designed to replace the FRC nitrogen with oxygen, and can normally be achieved to an end-tidal nitrogen concentration of 4% in 3 min in volunteers [5]. This increases the stores of oxygen within the body by the volume of the FRC. Obesity is associated with a decreased

FRC, which is reduced further by placing the patient in the supine position [6], allowing the tidal volume to approach and even fall within the closing capacity. Ideally, measurements of FRC, together with closing capacity, may produce better prediction of the effectiveness of preoxygenation in obese patients; however, these volumes are difficult to measure and are unlikely to be available routinely. All our patients achieved an Sp_{O_2} of 100 % within 30 s of the start of preoxygenation, indicating that the likely limitation is one of size of stored volume of oxygen in the body, rather than ability to reach that store, or to saturate the blood. This is supported by the blood-gas results.

This study illustrates further that awake tracheal intubation should be considered in any morbidly obese patient presenting for emergency surgery, especially those with expected difficulty in tracheal intubation, and preoperative bedside

lung function tests cannot be used to predict the effectiveness of preoxygenation.

REFERENCES

1. Robertson IK, Eltringham RJ. Anaesthetic management of the morbidly obese. *British Journal of Hospital Medicine* 1985; 34: 224-228.
2. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. *British Journal of Anaesthesia* 1988; 61: 211-216.
3. Samssoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; 42: 487-490.
4. Jenae HG, Dubin SA, Silverstein PI, O'Leary-Escolas U. Effect of obesity on duration of apnea in anesthetized humans. *Anesthesia and Analgesia* 1991; 72: 89-93.
5. Berthoud M, Read DH, Norman J. Pre-oxygenation—How long? *Anaesthesia* 1983; 38: 96-102.
6. Damia RW, Mascheroni D, Croci M, Tarenzi L. Preoperative changes in functional residual capacity in morbidly obese patients. *British Journal of Anaesthesia* 1988; 66: 574-578.

METABOLIC RESPONSE TO COLONIC SURGERY: EXTRADURAL VS CONTINUOUS SPINAL

J. WEBSTER, M. BARNARD AND F. CARLI

SUMMARY

We have examined the effect of intraoperative and postoperative (4 h) continuous spinal anaesthesia for colonic surgery on the postoperative glucose, lactate and cortisol responses. Twenty-one patients were studied; the first group (control) received general anaesthesia, the second group (extradural) an extradural block (T4-S5) and the third group (spinal) a continuous spinal block (T4-S5). Plasma concentration of glucose increased significantly in the control and extradural groups ($P < 0.05$) after surgery, with a small change in the spinal group. Plasma concentration of lactate increased significantly ($P < 0.05$) in the control group only. The postoperative increase in plasma concentration of cortisol was similar in both control and extradural groups, and significantly greater than that of the spinal group ($P < 0.05$). Thus continuous spinal analgesia attenuated, but did not abolish, the increase in plasma concentration of cortisol associated with colonic surgery.

KEY WORDS

Anaesthetic techniques: extradural, spinal. Metabolism: stress response. Surgery: colonic.

It has been well documented that extradural analgesia (T4-S5) for lower abdominal surgery inhibits glucose and cortisol responses [1]. However, results vary in studies of the effectiveness of extradural anaesthesia for colonic surgery in modulating the variables considered to be part of the stress response [2]. This might be caused by a partially effective neural afferent block.

The recent introduction of small-size spinal catheters has made possible the administration of low doses of local anaesthetics to establish a profound motor and sensory block during surgery with low risk of systemic toxicity caused by local

anaesthetics. The present study was designed to evaluate the effect of intraoperative afferent neural block, achieved with spinal local anaesthetics in patients undergoing colonic resection, on postoperative glucose and cortisol responses.

METHODS AND RESULTS

Twenty-one patients undergoing sigmoid colectomy for adenocarcinoma were allocated randomly to three groups of seven patients: control, extradural and spinal (mean ages 67 yr (range 57-73 yr), 71 yr (58-78 yr) and 69 yr (64-78 yr), respectively). Body mass index was comparable in the three groups. The study received Ethics Committee approval.

Premedication comprised papaveretum and hyoscine administered i.m. 60 min before surgery. All patients received general anaesthesia which consisted of thiopentone, pancuronium, enflurane, nitrous oxide and oxygen. In the extradural group patients, a catheter was inserted in the extradural space at T9-11 and segmental block (T4-S5) was established with 0.75 % bupivacaine 15 ml before induction of general anaesthesia. Additional 0.75 % bupivacaine 5-7 ml was administered every 45 min. At the end of surgery, the same extent of segmental analgesia was maintained with a continuous infusion of 0.25 % bupivacaine 10-15 ml h^{-1} . Patients in the spinal group received a continuous subarachnoid block via a spinal catheter (Kendall 28-gauge) at L2-3. After aspiration of CSF to confirm the position of the catheter, hyperbaric 0.5 % bupivacaine 2-3 ml was administered and segmental

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TABLE I. Mean (SD) plasma concentrations of glucose, lactate and cortisol in the three groups studied before and after surgery. Significant differences: * $P < 0.05$, ** $P < 0.01$ vs before surgery values; † $P < 0.05$, †† $P < 0.01$ vs control group

	Before surgery	End of surgery	After surgery (h)			
			1	2	3	4
Glucose (mmol litre ⁻¹)						
Control (n = 7)	5.5 (0.5)	9.5 (1.9)**	11.1 (3.4)**	11.0 (3.5)**	10.5 (3.1)**	9.9 (3.1)*
Extradural (n = 7)	5.4 (0.3)	6.6 (1.0)†	7.1 (1.3)†	6.0 (1.3)*†	7.1 (1.1)*†	7.1 (1.1)*†
Spinal (n = 7)	5.6 (1.1)	6.7 (1.1)†	7.3 (1.2)†	7.6 (1.5)†	7.2 (1.4)†	7.3 (1.6)
Lactate (mmol litre ⁻¹)						
Control (n = 7)	0.9 (0.3)	1.9 (0.9)*	2.0 (1.1)*	1.8 (1.0)*	1.9 (1.3)*	2.3 (1.7)*
Extradural (n = 7)	1.1 (0.2)	1.5 (0.8)	1.5 (0.9)	1.4 (0.8)	1.1 (0.6)	1.2 (0.5)
Spinal (n = 7)	1.2 (0.2)	1.1 (0.3)†	1.2 (0.5)	1.1 (0.3)	1.1 (0.2)	1.0 (0.2)
Cortisol (mmol litre ⁻¹)						
Control (n = 7)	297 (83)	1025 (104)**	1194 (88)**	1271 (154)**	1257 (239)**	1379 (196)**
Extradural (n = 7)	330 (81)	903 (244)**	1083 (420)**	1207 (349)**	1438 (382)**	1495 (382)**
Spinal (n = 7)	393 (174)	602 (206)*††	613 (208)*††	786 (217)**††	845 (237)**††	840 (256)**††

block (T4-S5) established before induction of anaesthesia. Additional hyperbaric 0.5% bupivacaine 0.5–1 ml was administered every 45 min. At the end of surgery, a continuous subarachnoid infusion of 0.25% bupivacaine 2–4 ml h⁻¹ was started and the same extent of analgesia maintained for 4 h. At the end of surgery the control group received a continuous s.c. infusion of papaveretum 2–5 mg h⁻¹. All patients received an i.v. infusion of 0.9% normal saline 6–8 ml kg⁻¹ h⁻¹. No blood products were used during the period of the study. Dextran 70 in 0.9% sodium chloride was administered when the blood loss exceeded 10% of the circulating volume.

On arrival of the patient in the anaesthetic room, a 16-gauge cannula was inserted under local anaesthesia in the right internal jugular vein and 20-ml samples of blood were taken before anaesthesia, at the end of surgery and 1, 2, 3 and 4 h after operation for measurement of plasma concentrations of glucose (hexokinase method), lactate (enzymatic assay, lactate dehydrogenase) and cortisol (radioimmunoassay). Power calculations were performed to determine the smallest difference between the spinal and the control groups that could be detected as significant at 5% level, with a between patient SD of any change as 10%. If seven patients were allocated to each group, a difference of approximately 15% between the groups could be detected. Analysis of variance was applied and comparisons were made within groups and between groups using Student's *t* test.

Mean duration of surgery was 175 min (range 125–240 min) and fluids administered amounted

to 2700 ml (range 1800–3850 ml). Ephedrine was required in only three patients (two in the spinal group and one in the extradural group); the maximum dose administered was 9 mg. The PCV decreased with surgery in all three groups (mean 16%, range 13–18%).

Plasma concentration of glucose increased in all groups after surgery; in the control and extradural groups the increase was significant at all times ($P < 0.05$), while in the spinal group it was just significant 2 h after surgery ($P = 0.05$) (table I). The control group had significantly greater plasma concentrations of glucose at each time than either the extradural or spinal groups. Plasma concentration of lactate in the control group increased significantly at all times after surgery. In contrast, no significant change was observed in the other groups. Plasma concentration of lactate in the control group was significantly greater ($P < 0.05$) than that in the spinal group at the end and 4 h after surgery. Plasma concentration of cortisol increased significantly ($P < 0.05$) after surgery in all three groups. The increase in the spinal group was significantly less than that in both extradural ($P = 0.02$) and control groups ($P = 0.007$). No significant difference was observed at any time between control and extradural groups.

COMMENT

This study has shown that the increase in plasma concentration of cortisol associated with colonic surgery may be attenuated, but not abolished, with spinal anaesthesia. The postoperative increase in plasma concentrations of glucose and

lactate with either spinal or extradural anaesthesia was less than that observed with the control group.

Spinal or extradural administration of local anaesthetics has been shown to prevent a major part of the classical endocrine-metabolic response to surgical procedures such as lower abdominal (for example gynaecological) surgery and operations on the lower extremities, but these techniques have been less effective for colonic surgery [2]. This is probably a result of differences in extradural or spinal analgesic techniques and dosage of local anaesthetic. However, it appears that by using large doses of local anaesthetics with sufficient sensory analgesia extending beyond the dermatomes of surgical procedure, there might be a pronounced inhibition of the stress response [3].

In this context, the attenuated increase in plasma concentration of cortisol observed at the end of surgery with spinal block, compared with extradural, could be explained by an effective, but not definite, preoperative neural block. More recently, the combined use of subarachnoid and extradural local anaesthetics have been reported

to inhibit the postinjury hypersensitivity to pain and abolish the increase in plasma concentrations of cortisol [4].

It remains to be seen if continuous spinal anaesthesia alone or in combination with other pain relief techniques leads to a significant effect on the stress response over a longer period of time.

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REFERENCES

1. Engquist A, Brandt MR, Fernandes A, Kehlet H. The blocking effect of epidural analgesia on the adrenocortical and hyperglycaemic responses to surgery. *Acta Anaesthesiologica Scandinavica* 1977; 21: 330-335.
2. Kehlet H. Surgical stress—the role of pain and analgesia. *British Journal of Anaesthesia* 1989; 63: 189-195.
3. Kehlet H. The stress response to surgery: release mechanisms and the modifying effect of pain relief. *Acta Chirurgica Scandinavica* 1988; (Suppl. 550): 22-28.
4. Dahl JB, Rosenberg J, Dirkes WE, Mogensen T, Kehlet H. Prevention of postoperative pain by balanced analgesia. *British Journal of Anaesthesia* 1990; 64: 518-520.

RAPID INHALATION INDUCTION WITH ISOFLURANE IN HUMIDIFIED CARRIER GAS

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SUMMARY

This study was designed to determine if rapid inhalation induction of anaesthesia (RII) with 5% isoflurane (4.5 MAC equivalent) in oxygen offers any advantage in terms of complication rate, speed of induction and patient acceptance in comparison with a previously described technique of RII using 2% isoflurane in nitrous oxide and oxygen. Forty ASA I and II unpremedicated patients were allocated randomly to receive RII with either 5% isoflurane in oxygen or 2% isoflurane and nitrous oxide in oxygen. The carrier gas was humidified in order to limit airway irritation associated with the use of isoflurane for inhalation induction. In this study the observed difference in mean induction time (7 s) between the two groups was neither clinically nor statistically significant. The groups were similar also with regard to complication rate and patient acceptance.

KEY WORDS

Induction: anaesthesia. Anaesthetics, volatile: isoflurane. Anaesthetics, gases: nitrous oxide.

Rapid inhalation induction of anaesthesia (RII) using isoflurane has been described previously [1, 2]. Because of the pungency of this agent, RII was performed in heavily premedicated patients [1] or else the inspired concentration of the agent was limited [2]. We have examined if 5% isoflurane (4.5 MAC) in oxygen offered any advantage in comparison with the technique described by Lamberty and Wilson [2], using 2% isoflurane and nitrous oxide in oxygen. This study was designed to compare the two techniques with regard to speed of induction, complication rate and patient acceptance in *unpremedicated* patients.

The carrier gas was humidified in order to limit airway irritation associated with inhalation induction with isoflurane [3].

METHOD AND RESULTS

After obtaining Ethics Committee approval and informed patient consent, we studied 40 ASA I and II unpremedicated patients presenting for day-case extraction of wisdom teeth by the same dental surgeon. The patients were allocated randomly to receive RII with 5% isoflurane in oxygen (group A) or 2% isoflurane in nitrous oxide and oxygen (group B).

All the inductions were carried out with an i.v. cannula *in situ* and monitoring comprising ECG, pulse oximetry (Ohmeda 4700 Oxicap, BOC Health Care, U.S.A.) and continuous non-invasive arterial pressure (AP) (Finapres, Ohmeda, BOC Health Care, U.S.A.). A newly-calibrated isoflurane vaporizer was adjusted by an assistant to deliver either 5% isoflurane in oxygen 6 litre min⁻¹ or 2% isoflurane in oxygen 2 litre min⁻¹ and nitrous oxide 4 litre min⁻¹. The Rotameters and backbar of the anaesthetic machine were covered by a green towel. All inductions were then carried out by one of the authors (P. van H.), who was unaware of the vaporizer and Rotameter settings.

Baseline measurements of heart rate (HR), AP and arterial oxygen saturation (Sp_{O₂}) were obtained before induction of anaesthesia. Patients

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TABLE I. Patient characteristics, details of inductions and cardiovascular variables (number, or mean (range or SD))

	Group A (n = 20)	Group B (n = 20)
Age (yr)	26 (17–55)	24 (14–38)
Sex (M/F)	12/8	14/6
Weight (kg)	63 (9)	62 (9)
ASA grade (no.)		
I	20	18
II	0	2
Smokers (no.)	7	8
Induction time (s)	121 (50)	134 (41)
No. of breaths to surgical anaesthesia	18 (12)	23 (8)
Complicated inductions (no.)	9	4
Coughing	3	0
Secretions	1	0
Excessive movement	6	4
Abandoned inductions	2	4
Mean arterial pressure (mm Hg)		
Before induction	94 (12)	97 (13)
At surgical anaesthesia	89 (14)	85 (10)
Heart rate (beat min ⁻¹)		
Before induction	76 (19)	80 (22)
At surgical anaesthesia	83 (18)	74 (18)
Postoperative interview (no.)		
Amnesia after VCB	16	14
Would repeat experience	17	17
Headache	1	1
Nausea and vomiting	0	0

were coached in the technique of taking a vital capacity breath (VCB) and then holding the breath for as long as comfortable before resuming spontaneous ventilation. The induction sequence commenced after the patient had understood the procedure.

Gas leaving the common gas outlet of the anaesthetic machine (temperature 20 °C, 15% relative humidity) passed through a water bath humidifier heated to 60 °C before entering the patient breathing system. Gas leaving the modified Mapleson A breathing system (as described by Lamberty and Wilson [2]) was at a temperature of 27 °C and a relative humidity of 98%.

The breathing system was primed by allowing the pre-set anaesthetic mixture to flow for 5 min before occluding the outlet of the system to allow both reservoir bags to fill, but not to become distended. The patient then took a VCB from the primed system and held the breath for as long as comfortable, before resuming spontaneous ventilation. The induction sequence studied included the time from the onset of VCB until stage 3, plane 1 of surgical anaesthesia was reached (no

response to verbal command, regular ventilation and central pupils). During the induction sequence, an assistant recorded mean arterial pressure (MAP), HR and SpO₂ before the onset of the VCB and at the onset of surgical anaesthesia. He also recorded induction time (onset of VCB to onset of surgical anaesthesia), number of breaths taken before the onset of surgical anaesthesia and any of the following complications: coughing (presence of a single cough); excessive secretions (secretions audible in the airway); laryngospasm; excessive movement (requiring restraint of the patient). All the time measurements were made by means of a stopwatch. Inhalation induction was abandoned if any of these complications threatened the safety of the patient—for example if the patient had repeated spasms of coughing.

After surgical anaesthesia had been achieved, suxamethonium was administered and tracheal intubation performed. Anaesthesia was maintained in all patients with 2% halothane and nitrous oxide in oxygen.

All the patients were visited 2 h after operation and asked about last conscious recall in the

induction sequence, if they would choose RII for any subsequent anaesthetics they may require, and if they had experienced any nausea, vomiting or headache.

The two groups were similar in characteristics (table I). The mean speed of induction between the two groups was not significantly different ($P = 0.443$). A point estimate of the ratio of the means (mean of speed of induction in group A *vs* mean speed of induction of the established technique, group B) was 94.8%, a reduction of only 5.2%. An interval estimate for this ratio is 72–117%.

There were more "complicated" inductions in group A (nine) than group B (four) (table I) (Fisher's exact test, $P > 0.05$). However, all the complicated inductions in group B had to be abandoned (all because of excessive movement), while only two of the nine complicated inductions in group A had to be abandoned (both because of uncontrolled coughing). In the inductions abandoned in both groups, all the patients smoked more than 20 cigarettes per day. There were no episodes of laryngospasm or desaturation in the groups (table I). There was a similar incidence of coughing, excessive movements and secretions in the two groups (table I). MAP and HR before induction and at the onset of surgical anaesthesia were not significantly different (paired and unpaired *t* test) within groups and between groups (table I).

The postoperative interview (table I) yielded similar responses from the two groups. Seventeen of the 20 patients in each group expressed the view that they would choose RII for a subsequent anaesthetic. Sixteen of the 20 patients in group A and 14 of the 20 patients in group B (Fisher's exact test, $P > 0.05$) had no recall of events after taking the VCB containing anaesthetic agent. There was a small incidence of headache and no nausea or vomiting. It should be noted that the responses of all the patients, including those in whom the induction had to be abandoned, are included in the results of the postoperative survey.

COMMENT

Theoretically, RII with isoflurane is an attractive technique for day-case anaesthesia because of the low blood-gas solubility coefficient of isoflurane [4]. This study has not shown any advantage of using 5% isoflurane in oxygen for RII in comparison with 2% isoflurane in nitrous oxide

and oxygen. In the case of an increase in speed of induction using 5% isoflurane, rather than 2% isoflurane and nitrous oxide in oxygen, only a 30–50% improvement would be clinically significant. If a 40% increase in speed of induction is taken to be clinically significant, for the present sample size the power of the *t* test is in excess of 90%. Therefore we conclude that there was no clinical difference in the mean speed of induction between the two groups.

The end-point of the induction sequence in this study was the onset of surgical anaesthesia. In our opinion, this is a more practical end-point than that used in other studies of RII, as this is the point at which body surface surgery may commence, or at which the patient may be paralysed and the trachea intubated.

The majority of patients had no recall of events after the VCB containing the anaesthetic agent. As far as most patients are concerned, this was truly a "single breath technique". Both techniques of RII were associated with a low incidence of reported adverse effects.

The severe coughing in the two patients in whom induction was abandoned in group A was in keeping with the experience of other authors using isoflurane for inhalation induction [5]. The greater incidence of excessive movement resulting in abandoned inductions in group B probably resulted from inclusion of nitrous oxide in the carrier gas. Because of its lower blood-gas solubility, nitrous oxide rapidly induces stage 2 of anaesthesia before isoflurane is able to induce stage 3 of anaesthesia.

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REFERENCES

1. Loper K, Reitan J, Benthuyzen J, Snook L. Comparison of halothane and isoflurane for rapid anesthetic induction. *Anesthesia and Analgesia* 1987; 66: 766–768.
2. Lamberty JM, Wilson IH. Single breath induction of anaesthesia with isoflurane. *British Journal of Anaesthesia* 1987; 59: 1214–1218.
3. van Heerden PV, Wilson IH, Marshall FPF, Cormack JR. Effect of humidification on inhalation induction with isoflurane. *British Journal of Anaesthesia* 1990; 64: 235–237.
4. Eger EI. The pharmacology of isoflurane. *British Journal of Anaesthesia* 1984; 56: 71S–97S.
5. Phillips AJ, Brimacombe JR, Simpson DL. Anaesthetic induction with isoflurane or halothane. *Anaesthesia* 1988; 43: 927–929.

UNSUSPECTED EXTRADURAL CATHETERIZATION IN AN INTERSCALENE BLOCK

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SUMMARY

A case report is described of a patient in whom a catheter was inserted inadvertently into the cervical extradural space in performing an interscalene brachial plexus block.

KEY WORDS

Anaesthetic techniques, regional: interscalene brachial plexus block. Complications: extradural catheterization

CASE REPORT

A 58-yr-old woman had a displaced fracture of her left radius. She developed a sympathetic dystrophy of the hand, with swollen, red tender fingers and secondary wasting of the forearm and hand muscles. She was admitted for intensive physiotherapy in an attempt to restore movement to her wrist and hand. However, this was difficult because of the intense pain when her hand was touched.

Several methods were attempted to provide analgesia for physiotherapy. Stellate ganglion blocks were not tolerated, as the patient found them to cause "excruciating" pain. A catheter inserted into the brachial plexus by the axillary route became dislodged. Daily "single shot" axillary blocks were successful, but the axilla became bruised and tender. A single shot interscalene block resulted in the ulnar distribution remaining unblocked, although the patient tolerated physiotherapy well. It was decided to insert a tunnelled interscalene catheter for a further 1 week of physiotherapy.

A 17-gauge over-the-needle cannula was used, as this was the smallest through which the 18-gauge catheter would pass. The interscalene space was entered perpendicularly at the level of the sixth cervical vertebra, as described by Winnie [1]. Paraesthesiae were elicited easily at a depth of

2 cm. The needle was withdrawn and the 18-gauge catheter inserted easily. In an attempt to position the tip in the lower part of the plexus, 12 cm was inserted. The proximal end was tunnelled subcutaneously to the anterior chest.

A plain x-ray of the neck did not reveal the catheter, as it was not radio-opaque.

Ten millilitre of 0.25% bupivacaine was injected. Within 5 min, the patient was pain free. Only the left hand and forearm were blocked. Six hours later the block was wearing off, and a further 0.25% bupivacaine 10 ml produced the same effect, with some spread to the left upper arm. Passive physiotherapy was performed easily and the patient was mobile and participated in ward activities.

The patient and physiotherapist commented on the excellent analgesia obtained.

After another top-up dose (10 ml), the patient experienced transient warmth in her *right* shoulder and numbness of her left arm. The catheter was withdrawn 3 cm. The following day, another top-up (0.25% bupivacaine 10 ml) resulted in postural hypotension (arterial pressure 115/70 mmHg with the patient lying, 80/? standing) and numbness spreading from the left hand to the neck and right shoulder.

As this seemed likely to have been caused by extradural spread, radiographic examination was undertaken.

Radiography

In the x-ray department, 2 ml of the water soluble, non-ionic contrast medium iopamidol (Niopam 200, Merck) was injected through the catheter (fig. 1). The patient was placed supine, with one pillow. The contrast may be seen outlining the intervertebral foramen at the level of

T1 and the lower part of the plexus sheath, and the catheter may be seen entering the extradural space at the level of C6-7. The contrast was seen to move rapidly cephalad, outlining the whole cervical extradural space.

In a film taken 2 min later (fig. 2), the contrast may be seen mainly at the C2 level.

The catheter was withdrawn 6 cm. A repeat film, taken the following day (fig. 3) with 3 ml of contrast, shows the sheath filling. There was no leakage into the extradural space.

Subsequently 0.25% bupivacaine 10 ml produced a good block of the shoulder and arm except the ulnar distribution.

The catheter was left *in situ* for a further 5 days, and produced good analgesia, with no more problems. It was removed intact, and the patient has had no sequelae, although 4 months later her sympathetic dystrophy was still troublesome.

DISCUSSION

Extradural block following interscalene block is well described [2-5]. Common to these reports is rapid spread of the block to the contralateral side, within 10-20 min. Most reports have described the use of large volumes (30-40 ml) of local anaesthetic, usually lignocaine.

In this case, the initial block was satisfactory and unilateral, but withdrawing the catheter produced a bilateral block. It seems likely that,



FIG. 1. Contrast in the intervertebral foramen (F). The catheter (C) can be seen entering the extradural space one interspace higher.

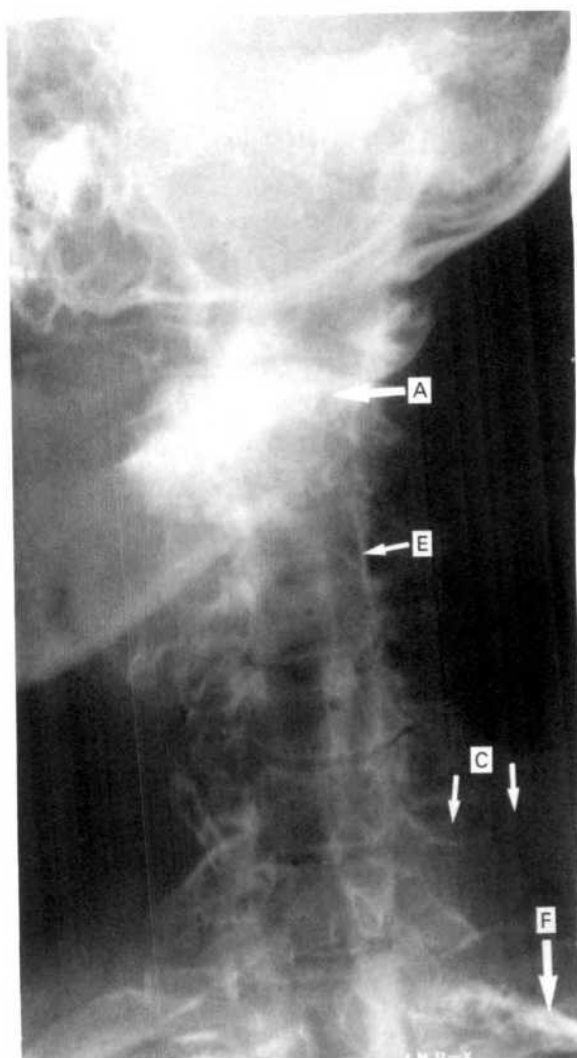


FIG. 2. Film taken 2 min after figure 1, 2 ml of contrast medium was used. Contrast has spread to the C2 level (A), outlining the cervical extradural space (E). The position of the catheter (C) and the intervertebral foramen (F) are marked.

during insertion, the catheter entered the extradural space at C6-7, and exited at C7-T1, re-entering the plexus sheath. This would explain the initial unilateral blocks. Withdrawal by 3 cm left the catheter tip in the intervertebral foramen (fig. 1), so local anaesthetic injected produced both a good block of the left arm, and a cervical extradural block.

Respiratory distress might be expected from a bilateral block including the roots of the phrenic nerve. In reports of bilateral block, this com-

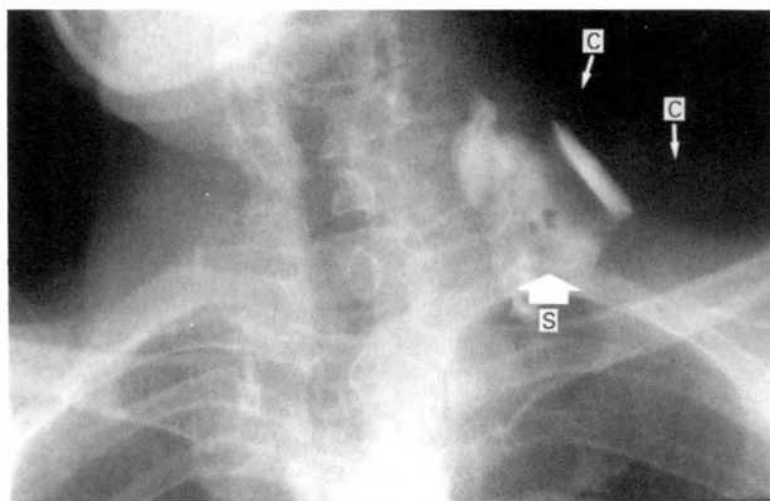


FIG. 3. Catheter withdrawn to correct position. The brachial sheath (S) is seen to fill, after injection of 3 ml of contrast medium. The catheter (C) is shown.

plication has been absent [2, 3], treated with oxygen [5], or required IPPV [4, 5]. Lombard [2] cited the absence of respiratory or cardiovascular depression as evidence that his patient's bilateral block was not caused by extradural spread.

There was no respiratory distress at any point in the present case, perhaps because of the small volume (10 ml) injected, and possibly the greater motor-sparing quality of bupivacaine. Hypotension occurred only when the patient stood, and therefore was detected only because she was ambulant.

In summary, this is a case where, despite extradural insertion of the catheter, a unilateral block was produced with no respiratory or cardiovascular signs of misplacement (until the patient stood erect).

In cannulation of the brachial plexus at this level, the direction of insertion of the catheter and the continuity with the cervical extradural space combine to make extradural insertion possible.

Either a radio-opaque catheter or fluoroscopy using a small volume of contrast medium may show correct (fig. 3) or ectopic (fig. 1) placement. Clinical results of injection of small volumes of local anaesthetic are an unreliable guide to correct placement, although the use of small doses should limit any effects.

REFERENCES

1. Winnie AP. Interscalene brachial plexus block. *Anesthesia and Analgesia* 1970; **49**: 455-466.
2. Lombard TP, Couper JL. Bilateral spread of analgesia following interscalene brachial plexus block. *Anesthesiology* 1983; **58**: 472-473.
3. Huang KC, Fitzgerald MR, Tsueda K. Bilateral block of cervical and brachial plexuses following interscalene block. *Anaesthesia and Intensive Care* 1986; **14**: 87-88.
4. Scammell SJ. Case report: Inadvertant epidural anaesthesia as a complication of interscalene brachial plexus block. *Anaesthesia and Intensive Care* 1979; **7**: 56-57.
5. Kumar A, Battit GE, Froese AB, Long MC. Bilateral cervical and thoracic epidural blockade complicating interscalene brachial plexus block: report of two cases. *Anesthesiology* 1971; **35**: 650-652.

SUPERIOR SAGITTAL SINUS THROMBOSIS AFTER INTERNAL JUGULAR VEIN CANNULATION

P. H. STEPHENS, G. LENNOX, N. HIRSCH AND D. MILLER

SUMMARY

A case of cerebral venous sinus thrombosis after central venous cannulation is presented. This occurred after a catheter had been in place for 5 days. The patient presented with thrombosis of the left internal jugular vein 4 days after removal of the catheter. Despite anticoagulation, the patient developed symptoms of increased intracranial pressure. Subsequently, a diagnosis of superior sagittal sinus thrombosis was made. The aetiology, diagnosis and management of this uncommon complication of central venous cannulation are discussed.

KEY WORDS

Complications: cerebral venous thrombosis. Veins: jugular cannulation

CASE REPORT

A 48-year-old woman with a benign oesophageal stricture presented for elective resection and colonic interposition. Her past medical history included epilepsy, diagnosed 10 yr previously, which was well controlled with phenytoin 100 mg three times daily. Initial blood results showed haemoglobin 128 g litre⁻¹, platelets 230×10^9 litre⁻¹ and normal coagulation studies. After induction of anaesthesia, two 14-gauge, 125-mm i.v. cannulae (Angiocath) were inserted via the "low" approach into the left internal jugular vein. The operation proceeded uneventfully via a left-sided thoracotomy. During surgery, prophylactic antibiotics (gentamicin, flucloxacillin and metronidazole) were given and the patient received a transfusion of blood 2 u via a peripherally sited cannula. The postoperative haemoglobin was 110 g litre⁻¹ and the platelet count was 180×10^9 litre⁻¹. After operation, one internal jugular venous catheter was left *in situ* for administration of total parenteral nutrition. This

was continued for 5 days, after which the internal jugular catheter was removed. Two days later, the patient was discharged home having made a good recovery.

Two days later the patient presented complaining of a tender, inflamed swelling with induration extending from the skin entry point of the catheter to the mastoid process. A clinical diagnosis of left internal jugular vein thrombosis was made and was confirmed after ultrasound examination. She was anticoagulated with heparin 1000 u h⁻¹ and warfarin therapy was commenced. However, over the course of the next 2 days she complained of frontal headaches, nausea and vomiting and became increasingly drowsy. A computed tomography (CT) examination of the head was performed which showed diffuse cerebral swelling with some cortical enhancement. A provisional diagnosis of increased intracranial pressure secondary to cerebral venous sinus thrombosis was made. The patient was treated with mannitol and transferred to our hospital for further management.

On arrival, she was drowsy but orientated. She complained of headache, and on examination there was restriction of upgaze and papilloedema. There were no other neurological signs. However, on turning her head to the right, she rapidly became unresponsive, with horizontal roving eye movements and developed bilaterally dilated but reactive pupils. These signs resolved immediately on rotating her head to the left. A similar episode occurred when the head was elevated by 20°. CT examination of the head was repeated and on this occasion post enhancement study showed the characteristic "empty delta" sign, a finding

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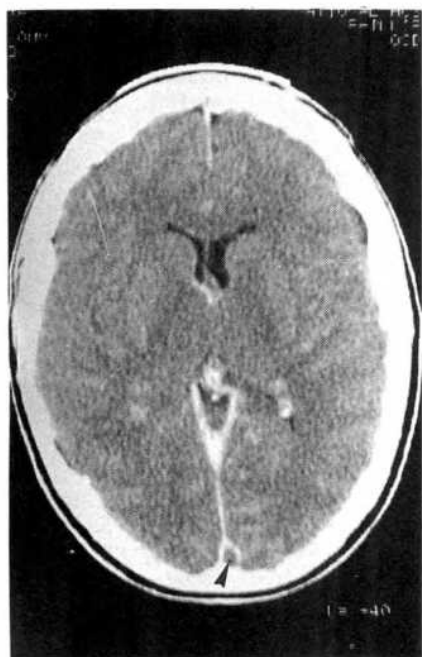


FIG. 1. Post enhancement CT of the head. There is a filling defect in the superior sagittal sinus (arrow), diagnostic of superior sagittal sinus thrombosis.

pathognomonic of superior sagittal sinus thrombosis [1] (fig. 1). In addition, thrombosis of the left transverse sinus was demonstrated. Digital subtraction venous angiography via the left arm confirmed extensive thrombus in the left internal jugular and brachiocephalic veins (fig. 2).

Heparin therapy was continued, but over the next 48 h the platelet count decreased from 180 to $59 \times 10^9 \text{ litre}^{-1}$. Fibrin degradation products were normal and heparin was assumed to be responsible for her thrombocytopenia. Heparin was discontinued and anticoagulation was continued with warfarin, after which the platelet count increased. In addition, in view of a possible infective component to the thrombosis, i.v. antibiotics (flucloxacillin and amoxycillin) were commenced. Intracranial hypertension was managed with dexamethasone, acetazolamide and mannitol. Over the next 48 h, the patient's symptoms improved markedly, although papilloedema was still present. In addition, there was partial resolution of the inflammation and swelling in her neck, although the internal jugular vein remained indurated to palpation. Warfarin and acetazolamide were continued. Over the next 2 months, severe papilloedema persisted with marked enlargement

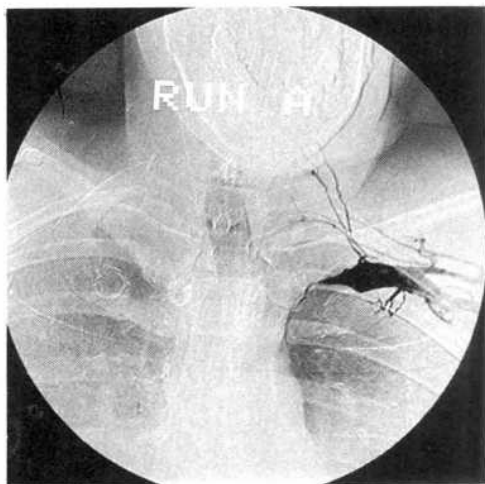


FIG. 2. I.v. digital subtraction angiogram. There is complete occlusion of the left subclavian vein, with extensive collateral formation via intercostal and internal mammary branches.

of the blind spots. Visual acuity remained stable at 6/5 in both eyes.

At latest follow up, after 3 months, the papilloedema was beginning to resolve, and the area of residual induration in the left side of the neck was smaller.

DISCUSSION

Asymptomatic thrombosis (i.e. the presence of a sleeve of fibrin around a catheter or thrombus adherent to a vessel wall) is not uncommon after central venous cannulation. A recent study has suggested an incidence as high as 70% [2]. Factors thought to contribute to the development of thrombosis are duration of cannulation, position of the catheter tip, physical properties of the catheter and nature of infused fluid. Our patient may therefore be considered to have been at high risk of developing thrombosis as a relatively rigid catheter, proximal to the right atrium, was used to infuse hyperosmolar total parenteral nutrition solution.

However, despite the apparent high incidence of local thrombosis around catheter tips, symptomatic antegrade and retrograde extension of thrombus is rare. Factors which may predispose to extension of thrombus, when initiated, are infection, intrinsic abnormalities of coagulation and relative intravascular stasis. Similar considerations apply to the aetiology of cerebral sinus thrombosis.

Despite the temporal relationship between the institution of antibiotic therapy and clinical improvement in our patient, no unequivocal evidence of infection could be obtained, although she exhibited a low grade fever (37.5°C) and a slight polymorph leucocytosis ($11-17 \times 10^9 \text{ litre}^{-1}$). No growth was obtained from blood cultures. There were no other sources of local infection described classically as causing cerebral venous thrombosis, such as chronic otitis media, tonsillitis and osteomyelitis.

Several other conditions may predispose to dural sinus thrombosis [3]. These include pregnancy and the puerperium, transfusion reactions, polycythaemia, thrombocythaemia, haemolytic anaemia, sickle cell disease, collagen vascular disorders (systemic lupus erythematosus and Behçets syndrome), inflammatory bowel disease, lupus anticoagulant, protein S deficiency, antithrombin 3 deficiency, cryofibrinogenaemia and oestrogen therapy. None of these conditions was present in our patient.

A relatively hypercoagulable state exists after operation [4] and this may be exacerbated by hypotension and increases in blood viscosity secondary to dehydration and haemoconcentration. This may have predisposed to formation of thrombus in our patient. Although rare, cerebral sinus thrombosis has been reported as following central venous cannulation [5, 6].

However, in previous cases this has been associated with probable retrograde flow of hyperosmolar total parenteral nutrition solution in the internal jugular vein after catheter misplacement in the region of the jugular bulb. In addition, cerebral sinus thrombosis has followed placement of pacing wires [7, 8] and ligation of the internal jugular vein [9]. The relative rarity of cerebral symptoms after occlusion of the jugular vein may be explained in part by the presence of numerous anastomotic channels associated with the venous drainage of the head. However, these are not a constant feature. It is interesting to note that our patient appeared to perform a variation of Crowe's Test (compression of the contralateral jugular vein causing unilateral facial venous engorgement) for transverse sinus thrombosis [10] when she turned her head to the right.

The anatomy of the region of the confluence of the sinuses is variable [11]. In the majority of cases the superior sagittal sinus drains into the right transverse sinus and thence to the right internal jugular vein. In only 8% of cases does the

superior sagittal sinus drain exclusively into the left transverse sinus and thence to the left internal jugular vein. It is therefore of interest that our patient showed superior sagittal sinus thrombosis in association with left transverse sinus thrombosis.

Classically, the features of superior sagittal sinus thrombosis are those of increased intracranial pressure caused by obstruction of venous and cerebrospinal fluid outflow. Fever may occur. Less commonly, convulsions and focal neurological deficits arise from associated haemorrhagic infarction [3].

Although the diagnosis may be suspected on clinical grounds it should be confirmed by angiography, CT [12] or magnetic resonance [13] imaging. Non-specific, unenhanced CT findings include ventricular compression and haemorrhagic infarction, although initially the examination may be normal. The "empty delta" sign seen on post enhancement CT is present in only 30% of cases but when seen, confirms the diagnosis [1].

Prognosis of dural sinus thrombosis is difficult to evaluate, as it is related to the aetiology. Mortality has been reported as 5-80%. In general, mortality appears to be declining as infection becomes a less prominent aetiological factor and since the advent of antibiotics. Adverse prognostic features include coma, infection, cerebral venous extension, cerebral infarction and seizures [3].

The role of anticoagulation in cerebral venous sinus thrombosis is uncertain [14]. In the presence of haemorrhagic infarction, it should be avoided. However, at least one controlled study has demonstrated benefits from anticoagulation [15]. In our patient, in whom there was extensive dural sinus thrombosis without CT evidence of cerebral infarction, it was thought that the potential benefits outweighed the risks. Thrombolytic therapy for venous thrombosis using streptokinase or urokinase is being evaluated [16, 17], but cannot be recommended routinely at this time, and was considered inappropriate in our patient in view of her recent bowel anastomosis.

REFERENCES

1. Virapongse C, Cazenave C, Quisling R, Sarwar M, Hunter S. The empty delta sign: frequency and significance in 76 cases of dural sinus thrombosis. *Radiology* 1987; 162: 779-785.
2. Yagi K, Kawakami M, Sugimoto T. A clinical study of thrombus formation associated with central venous catheterization. *Nippon Geka Gakkai Zasshi* 1988; 89: 1943-1949.

3. Lefkowitz D. Cortical thrombophlebitis and sinovenous disease. In: Toole JF, ed. *Handbook of Clinical Neurology*. Amsterdam: Elsevier, 1989; 395-423.
4. Grant PG, Tate GM, Williams NS, Davies JA, Prentice CRM. Intraoperative activation of coagulation—a stimulus to thrombosis mediated by vasopressin. *Thrombosis and Haemostasis* 1988; 55: 104-107.
5. Saxena VK, Heilpern RS, Murphy SF. Pseudotumour cerebri: a complication of parenteral hyperalimentation. *Journal of the American Medical Association* 1976; 235: 21-24.
6. Souter RG, Mitchell A. Spreading cortical venous sinus thrombosis due to infusion of hyperosmolar solution into the internal jugular vein. *British Medical Journal* 1982; 285: 935-936.
7. Girard DE, Reuter JB, Mayer BS, Nardone DA, Jendrzewski J. Cerebral venous sinus thrombosis due to indwelling transvenous pacemaker catheter. *Archives of Neurology* 1969; 37: 113-114.
8. Floyd WL, Mahaley MS. Cerebral dural sinus thrombosis following cardiac pacemaker implantation. *Archives of Internal Medicine* 1969; 124: 368-372.
9. Marr WG, Cambers RG. Pseudotumour cerebri: syndrome following radical neck dissection. *American Journal of Ophthalmology* 1961; 51: 605-615.
10. Smith BH. Infections of the dura and its venous sinuses. In: Baker AB, Baker LH, eds. *Clinical Neurology*. Philadelphia: Harper and Row, 1984; 1-34.
11. Brouder J, Kaplan HA. *Cerebral Dural Sinuses and Their Tributaries*. Springfield, Illinois: Charles C. Thomas, 1979.
12. Grosman H, St Louis EL, Gray RR. The role of CT and DSA in cranial sino-venous occlusion. *Canadian Association of Radiologists Journal* 1987; 38: 183-189.
13. Hulcelle PJ, Dooms GC, Mathurin P, Cornelis G. MRI assessment of unsuspected dural sinus thrombosis. *Neuroradiology* 1989; 31: 217-221.
14. Humphrey PRD, Clarke CRA, Greenwood RJ. Cerebral venous thrombosis. In: Harman MJG, Dyker ML, eds. *Cerebral Vascular Disease*. London: Butterworths, 1983; 309-319.
15. Villinger A, Garner C, Meister W, Haberl R, Pfister W, Einhaeupl KM. High dose heparin treatment in cerebral venous occlusive disease. *Stroke* 1988; 19: 135.
16. Halevy A, Leonov Y, Lewinsohn G, Witz E, Orda R. Thrombosis of superior vena cava during total parenteral nutrition, managed successfully with low dose streptokinase. *Intensive Care Medicine* 1988; 14: 72-73.
17. Di Roccio C, Iannelli A, Leone G, Moschini M, Valori VM. Heparin-urokinase treatment in aseptic dural sinus thrombosis. *Archives of Neurology* 1981; 38: 431-435.

DELAYED PNEUMOTHORAX AFTER SUBCLAVIAN VEIN CATHETERIZATION AND POSITIVE PRESSURE VENTILATION†

M. C. CRONEN, P. W. CRONEN, P. ARINO AND K. ELLIS

SUMMARY

Delayed pneumothorax may occur after subclavian vein catheterization and results from slow accumulation of air in the pleural space. Thus initial postinsertion chest x-rays may not detect this complication. The addition of positive pressure ventilation for general anaesthesia may make this complication life threatening. We report three cases and the literature is surveyed.

KEY WORDS

Complications: delayed pneumothorax. Veins: subclavian catheterization.

Pneumothorax after subclavian vein catheterization is a well documented complication that may occur in 1-10 % of all catheter insertions [1]. While it is standard practice to obtain a chest x-ray after catheterization to confirm placement and to exclude complication, initial films may fail to show a pneumothorax. A delayed pneumothorax may occur from 8 h to 4 days after insertion. We have experienced three instances in which pneumothorax followed insertion of a central venous catheter and positive pressure ventilation for general anaesthesia.

CASE REPORTS

Patient 1

A 68-yr-old woman with gastrointestinal bleeding and hypotension underwent rapid fluid and red cell infusions via peripheral veins. After stabilization, a left subclavian vein catheterization was attempted, but was unsuccessful. A left internal jugular catheter was inserted. Chest x-ray showed the catheter to be in good position and a pneumothorax was not present. Six hours after

bowel resection for continued gastrointestinal blood loss, the patient became moderately hypotensive with an arterial pressure of 90 mm Hg. Decreased breath sounds were noted on the left side. Volume infusion corrected the presumed volume deficit, but a chest x-ray later that day showed a pneumothorax. Closed thoracostomy was performed.

Patient 2

A 54-yr-old white female with inflammatory bowel disease underwent parenteral alimentation for nutritional support before bowel resection. A left subclavian catheter was inserted after multiple attempts. The initial chest film did not show any abnormality. Two days later, during the operation, the patient's arterial pressure decreased to 70 mm Hg. This responded to infusion of fluids. Hypotension recurred in the recovery room and a chest x-ray was obtained which showed a left tension pneumothorax. A chest drain was inserted and the patient's symptoms resolved.

Patient 3

A 63-yr-old man with rectal carcinoma had a right subclavian catheter inserted 2 days before an abdomino-perineal resection. No abnormality was noted on chest x-ray after the procedure. During operation, the patient became hypotensive with

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TABLE I. Delayed pneumothorax: summary of case reports in the literature. n/a = Not available by case from report: 75% overall. PPV = Positive pressure ventilation

Authors	Presentation (days after insertion)	Insertion difficult	Patient sympto- matic	PPV
Lewis [1]	1.0	—	—	—
Mitchell and Steer [2]	5.0	+	+	—
Slezak and Williams [3]	1.0	+	+	—
	0.1	+	+	—
	1.5	+	—	—
Plaus [4]	0.3	n/a	+	—
	0.7	n/a	+	—
	0.7	n/a	+	—
	3.0	n/a	+	—
	4.0	n/a	+	—
Sivak [5]	2.0	—	+	—
	4.0	—	+	—
Present study	1.0	+	+	+
	2.0	+	—	+
	3.0	+	—	+

low central venous pressures, suggesting hypovolaemia. Hypoxaemia then occurred. The operation was completed hurriedly and a chest x-ray was obtained immediately after operation; this revealed a right tension pneumothorax. Insertion of a chest drain relieved the patient's symptoms.

DISCUSSION

These three anecdotal cases illustrate the fact that delayed pneumothorax after insertion of a central venous catheter may occur with positive pressure ventilation. We postulate that a small visceral pleural laceration occurred at the time of catheterization which was not large enough to cause a detectable pneumothorax on the initial post-insertion chest film, or the laceration sealed promptly. With time, either slow accumulation of air occurred in the pleural cavity and was accelerated with positive pressure ventilation, or re-opening of the laceration occurred, causing a symptomatic pneumothorax. The presenting feature of all three cases was haemodynamic instability in the intraoperative or early post-operative phase. In all subjects, the facts that initial chest films were normal and that volume infusion initially improved the haemodynamic situation led the physicians to look for alternative causes. It is noteworthy that insertion of the catheter was difficult in two of the three patients.

Signs of pneumothorax may be masked during anaesthesia. Auscultation may not reveal decreased breath sounds and a tracheal shift may not be apparent because of mechanical ventilation, indwelling tubes or patient position. Tachycardia and hypotension, as in our cases, may be the initial signs and suggest hypovolaemia rather than pneumothorax. A bulging hemidiaphragm during intra-abdominal procedures may be a clue to the diagnosis.

While delayed pneumothorax from insertion of a central venous catheter is probably not infrequent, there are few descriptions of this complication. Mitchell and Steer reported a case occurring in a patient before operation [2]. They recommended that a chest x-ray should be obtained before operation in any patient with a central venous catheter. Slezak and Williams have reported three cases of delayed pneumothorax [3]. In all patients, insertion of a catheter was difficult, and two of the three had complaints of chest pain on the side of the insertion. None occurred with positive pressure ventilation. Lewis [1] has reported one additional case in which the patient was asymptomatic. Plaus has reported the largest series, with five cases and, from a retrospective review at his institution [4], estimated an incidence of symptomatic delayed pneumothorax of 4.1%. Difficulty in catheterization was noted in 75% of all cases of pneumothorax. None occurred with positive pressure. In Sivak's report of two cases, it was recommended that a preoperative chest x-ray be obtained in all patients with a central venous catheter [5].

Based on these 12 and our three case reports (table I), we would suggest that a repeat chest x-ray should be obtained: (1) in all patients in whom catheterization was difficult, including those patients in whom suspected pleural entry occurred (air aspiration, chest pain) but in whom the initial chest film was negative; (2) when haemodynamic instability occurs during operation and seems out of proportion to fluid and blood loss; (3) in any patient with clinical symptoms of pneumothorax (chest pain, respiratory difficulty, or shoulder tip pain). In addition, routine delayed chest film may be advisable in any patient with an existing central venous catheter.

REFERENCES

1. Lewis ES. Delay pneumothorax: A complication of subclavian vein catheterization. *Journal of Parenteral and Enteral Nutrition* 1986; 10: 542-543.

2. Mitchell A, Steer HW. Late appearance of pneumothorax after subclavian vein catheterization: An anaesthetic hazard. *British Medical Journal* 1980; **281**: 1339.
3. Slezak FA, Williams GB. Delayed pneumothorax: A complication of subclavian vein catheterization. *Journal of Parenteral and Enteral Nutrition* 1984; **8**: 571-574.
4. Plaus WJ. Delayed pneumothorax after subclavian vein catheterization. *Journal of Parenteral and Enteral Nutrition* 1990; **14**: 414-415.
5. Sivak SL. Late appearance of pneumothorax after subclavian venipuncture. *American Journal of Medicine* 1986; **80**: 323-324.

REPAIR OF TRAUMATIC TRANSECTION OF THE THORACIC AORTA: ESMOLOL FOR INTRAOPERATIVE CONTROL OF ARTERIAL PRESSURE

S. G. FENNER, A. MAHONEY AND J. N. CASHMAN

SUMMARY

We report the intraoperative use of esmolol for control of arterial pressure during repair of a traumatic transection of the descending thoracic aorta. A mean infusion rate of esmolol 50.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ resulted in a decrease in mean arterial pressure to 63 mm Hg and heart rate to 99 beat min^{-1} and was associated with excellent surgical conditions. The infusion rate of esmolol was titrated easily against mean arterial pressure, which increased rapidly on discontinuing its infusion. Control of arterial pressure with esmolol was comparable to that achieved with sodium nitroprusside, but without the reflex tachycardia or decrease in PaO_2 associated with the latter agent.

KEY WORDS

Anaesthetic techniques: induced hypotension. Arterial pressure: esmolol, sodium nitroprusside. Surgery: aortic transection.

CASE REPORT

A previously healthy 20-yr-old man was admitted to hospital following a road traffic accident. Clinical and radiological examinations at the referring hospital had revealed multiple fractures, central abdominal peritonism, but no evidence of significant head or chest injury. After resuscitation with i.v. fluids, laparotomy was performed and damaged small bowel and mesentery were resected, his fractured right elbow was stabilized in plaster of Paris and a right distal tibial traction pin was inserted. On the first day after operation the patient complained of central chest pain and another chest x-ray revealed widening of the superior mediastinum. A provisional diagnosis of intrathoracic aortic transection was made.

The patient was transferred to this Regional Cardiothoracic Unit for investigation and management of suspected intrathoracic aortic injury. On his arrival, assessment revealed a conscious patient with an arterial pressure of 110/70 mm Hg, heart rate 100 beat min^{-1} , normal peripheral pulses and good urine output. A subsequent arch aortogram revealed a leak of contrast just distal to the left subclavian artery, consistent with transection of the descending thoracic aorta. The patient was transferred immediately to the operating theatre for repair of this defect via a left thoracotomy.

In the anaesthetic room, the right radial and posterior tibial arteries were cannulated for measurement of proximal and distal arterial pressures during aortic cross-clamping. A 7-French gauge thermodilution pulmonary artery catheter (American Edwards Laboratories) was placed via the right internal jugular vein. In the operating theatre full invasive haemodynamic monitoring was commenced during preoxygenation. Anaesthesia was induced with diamorphine 200 $\mu\text{g kg}^{-1}$ i.v. followed by thiopentone 2 mg kg^{-1} i.v. Suxamethonium 1.5 mg kg^{-1} i.v. was administered to facilitate intubation with a 37-French gauge left-sided double-lumen endobronchial tube. Further increments of diamorphine were given to a total dose of 400 $\mu\text{g kg}^{-1}$

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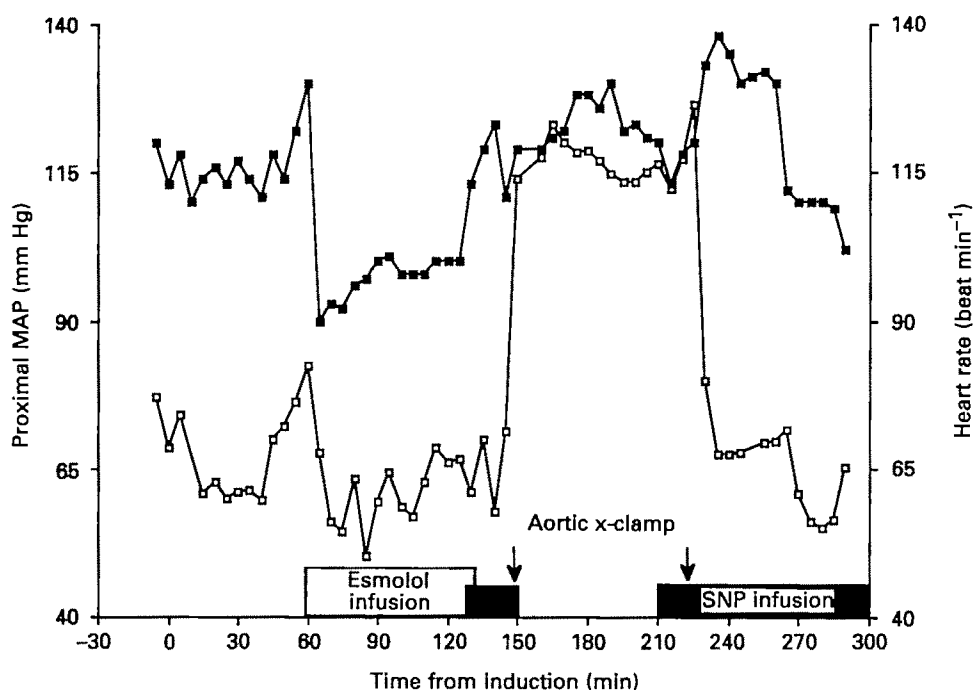


FIG. 1. Heart rate (■) and proximal MAP (□) changes during anaesthesia for repair of aortic rupture, showing their relation to aortic cross-clamping and to the infusions of esmolol and SNP.

i.v. Anaesthesia during the 5-h procedure was maintained by intermittent positive pressure ventilation with 25–50% nitrous oxide and enflurane in oxygen with intermittent boluses of fentanyl (total $15 \mu\text{g kg}^{-1}$ i.v.) and pancuronium (total $250 \mu\text{g kg}^{-1}$ i.v.). It was decided to use an i.v. infusion of esmolol (Brevibloc-Dupont Pharmaceuticals) to control systemic arterial pressure during aortic dissection, before aortic cross-clamping. The authors were interested also to compare the cardiovascular conditions provided by esmolol with those provided by sodium nitroprusside (SNP) (currently our preferred agent for the intraoperative control of arterial pressure). Therefore, after 1 h the infusion of esmolol was changed to an i.v. infusion of SNP.

During the course of surgery cardiac output, pulmonary artery pressures, pulmonary capillary wedge pressures (PCWP) and arterial blood-gas measurements were recorded at intervals in addition to the usual variables recorded during an intrathoracic vascular procedure. After induction of anaesthesia, arterial pressure stabilized at 80/55 mm Hg with a heart rate of 110–120 beat min⁻¹. However, within 15 min of the commencement of surgery, arterial pressure and heart rate had

increased to 130/60 mm Hg and 140 beat min⁻¹, respectively. At this point an infusion of esmolol $150 \mu\text{g kg}^{-1} \text{min}^{-1}$ was commenced without a bolus loading dose. This produced a rapid decrease in heart rate and arterial pressure to 95 beat min⁻¹ and 80/45 mm Hg, respectively (figs 1, 2). During the next 60 min of one lung-ventilation, before aortic cross-clamping, the infusion of esmolol was adjusted to maintain mean arterial pressure (MAP) at an average of 63 mm Hg, with an average heart rate of 99 beat min⁻¹ (fig. 1).

After esmolol was discontinued, MAP was controlled for the remaining 20 min before application of the aortic cross-clamps with an infusion of SNP which was commenced at a rate of $1.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ (fig. 1). This produced a rapid decrease in arterial pressure to 72/44 mm Hg (fig. 2), but was associated with an increase in heart rate to 125 beat min⁻¹ (fig. 1). There was an increase in cardiac index during infusion of SNP compared with values obtained both before induction and during the infusion of esmolol. Arterial blood-gas measurements revealed a decrease in P_{aO_2} from 10 kPa before infusion of SNP to 7.7 kPa during infusion of SNP, despite unchanged ventilation and inspired oxygen concentration.

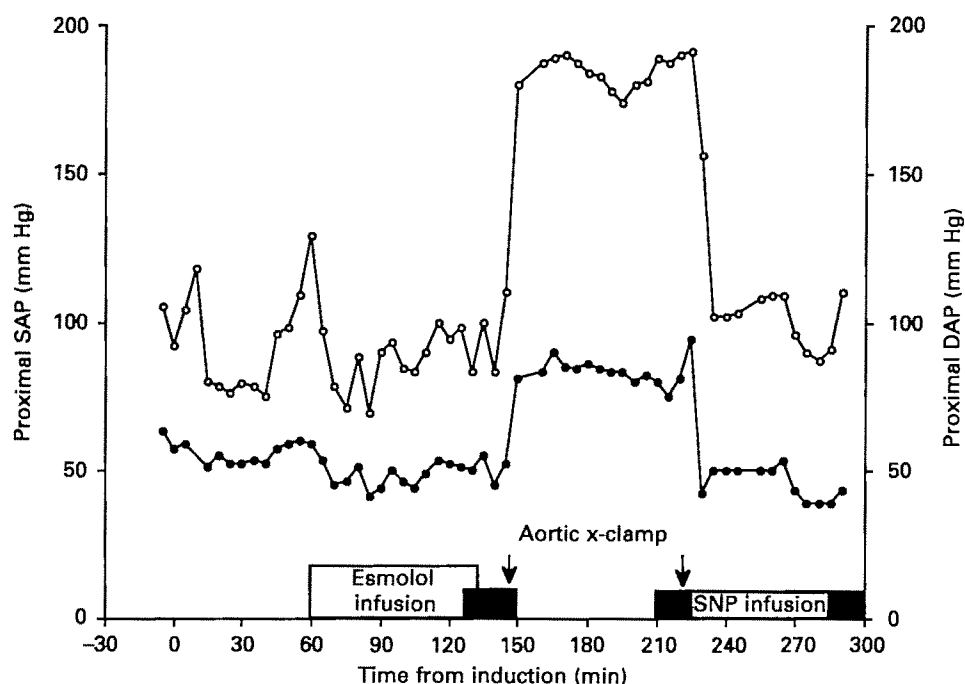


FIG. 2. Proximal systolic (SAP) (○) and diastolic (DAP) (●) arterial pressures during anaesthesia for repair of aortic rupture, showing their relation to aortic cross-clamping and to the infusions of esmolol and SNP.

TABLE I. Proximal mean arterial pressures (MAP), pulmonary capillary wedge pressures (PCWP), cardiac indices and systemic arterial oxygen partial pressures (Pa_{O_2}) in relation to intraoperative events and drug infusions during repair of transected thoracic aorta. OLV = One lung ventilation; x-clamp = aortic cross-clamps applied; n/a = not available

Time (min)	MAP (mm Hg)	PCWP (mm Hg)	Cardiac index (litre $\text{min}^{-1} \text{m}^{-2}$)	Arterial Pa_{O_2} (kPa)	Drug infusions	Events
-5	77	n/a	4.50	n/a	Nil	Before induction
75	54	11	3.21	10.00	Esmolol $60 \mu\text{g kg}^{-1} \text{min}^{-1}$	OLV
135	70	12	5.90	12.40	Nil	OLV + x-clamp
175	118	12	4.94	n/a	Nil	OLV + x-clamp
285	56	6	5.12	7.70	SNP $1.2 \mu\text{g kg}^{-1} \text{min}^{-1}$	OLV

Cardiac index measurements, arterial Pa_{O_2} , MAP and PCWP obtained before induction, during the infusion of esmolol, during aortic cross-clamping and during the infusion of SNP are shown in table I.

The aortic cross-clamps were applied for 75 min, during which time the 95% transection of the descending aorta was repaired with a 16-mm Gelseal (Vascutek) graft whilst distal perfusion pressure (measured at the right posterior tibial

artery) was maintained with a 7-mm Gott shunt (Argyle). At the surgeon's request, SNP was discontinued after aortic cross-clamping in order to maintain distal arterial pressure, which had decreased rapidly after the application of the cross-clamps. Distal MAP stabilized at 50 mm Hg after stopping SNP; proximal MAP was 117 mm Hg. The infusion of SNP was recommenced just before the aortic cross-clamps were released and was adjusted to achieve a proximal

MAP of 60–70 mm Hg. Unfortunately, this was associated with an increase in heart rate from an average of 123 beat min⁻¹ during aortic cross-clamping to 132 beat min⁻¹ after the cross-clamps had been released. A reduction in this heart rate was achieved before the end of surgery by administration of three increments of labetalol 10 mg i.v.

After operation the lungs were ventilated mechanically for 48 h and the patient sedated with an i.v. infusion of papaveretum and intermittent i.v. bolus doses of diazepam. Arterial pressure was controlled with i.v. infusions of labetalol and SNP. During this period the patient underwent a 12-h orthopaedic operation for internal fixation of his fractured long bones. The patient was discharged eventually back to the referring hospital 4 days after the aortic repair.

DISCUSSION

Esmolol is an ultra-short acting β_1 -adrenoceptor antagonist. In normal subjects after i.v. administration, it has distribution and elimination half-lives of only 2 min and 9 min [1], respectively. Esmolol has a rapid onset of action: an effect on heart rate is observed within 3 min [2]. It is metabolized rapidly, predominantly by erythrocyte esterases, to an acid metabolite (a 1500-fold less potent adrenoceptor antagonist than esmolol) and methanol. Plasma cholinesterases are not involved in the metabolism and there is thus no significant effect on the inactivation of suxamethonium [3, 4]. Less than 1% of an administered dose of esmolol is recovered unchanged in the urine; more than 70% of the acid metabolite is recovered from the urine [5]. Esmolol has been shown to be effective in attenuating the hypertension and tachycardia resulting from laryngoscopy and tracheal intubation [2, 6, 7], for the control of intraoperative hypertension and tachycardia [7, 8] and has been used effectively as part of the management of arterial pressure during resection of pheochromocytoma [9]. In addition, esmolol has been used successfully to control atrial tachyarrhythmia [10] and in the management of angina pectoris [11].

The authors are unaware of any previous report of the use of esmolol to control arterial pressure during surgery to repair transection of the thoracic aorta. In such cases, control of arterial pressure is important before application of aortic cross-clamps in order to prevent further aortic dis-

ruption and haemorrhage [12]. Furthermore, it is important after application of the cross-clamps in order to prevent acute left ventricular failure [12]. Even at relatively low infusion rates, esmolol proved to be extremely effective in controlling this patient's arterial pressure before aortic cross-clamping. The effect of esmolol on arterial pressure was adjusted easily because of its short elimination half-life. The negative chronotropic effect of esmolol in this patient was observed clearly when compared with SNP, which produced tachycardia. This effect of esmolol may be of considerable advantage in patients with ischaemic heart disease, in whom the tachycardia and reduced coronary artery perfusion pressure produced by SNP may impair the myocardial oxygen supply and demand relationship, which may in turn be associated with myocardial ischaemia [8, 13]. The negative chronotropic effect of esmolol may also be useful in younger patients who usually exhibit marked compensatory tachycardia when controlled hypotension is induced with an arteriolar dilating agent such as SNP. Furthermore, SNP causes a much greater decrease in diastolic arterial pressure than esmolol [14]. This may have important implications for maintenance of coronary and renal artery perfusion pressures. A further undesirable action of SNP is its effect on hypoxic pulmonary vasoconstriction (HPV). Esmolol has no discernible effect upon HPV, demonstrated by minimal changes in PCWP and P_{aO_2} , as opposed to SNP which causes decreases in both [14]. We were interested to observe these differences between esmolol and SNP in our patient (table 1).

Esmolol is relatively contraindicated in patients with left ventricular dysfunction, as it may reduce cardiac output further. Sodium nitroprusside usually causes an increase in cardiac output (as seen here) and therefore may be the preferred agent in this situation [14]. Some of the disadvantages of using SNP may be attenuated by concomitant use of a β -adrenoceptor antagonist such as propranolol or the mixed α - and β -adrenoceptor antagonist, labetalol [12, 15]. Both of these agents have elimination half-lives which are substantially longer than those of esmolol or SNP, making fine control of arterial pressure and heart rate during anaesthesia unpredictable and difficult to achieve. Any deleterious effects of β -adrenoceptor antagonism, caused by esmolol, should resolve quickly and spontaneously as a result of its rapid metabolic breakdown. A more

logical approach to control of arterial pressure during anaesthesia and surgery for cases such as this might be to use infusions of a short-acting vasodilating agent such as SNP in combination with an ultra-short acting β -adrenoceptor antagonist such as esmolol.

REFERENCES

1. Sum CY, Yacobi A, Kartzinel R, Stampfli H, Davis CS, Lai C-M. Kinetics of esmolol, an ultra-short-acting beta blocker, and of its major metabolite. *Clinical Pharmacology and Therapeutics* 1983; 34: 427-434.
2. Menkhaus PG, Reves JG, Kissin I, Alvis JM, Govier AV, Samuelson PN, Lell WA, Henling CE, Bradley E. Cardiovascular effects of esmolol in anesthetized humans. *Anesthesia and Analgesia* 1985; 64: 327-334.
3. McCammon RL, Hilgenberg JC, Sandage BW, Stoelting RK. The effect of esmolol on the onset and duration of succinylcholine-induced neuromuscular blockade. *Anesthesiology* 1985; 63: A317.
4. Gorczynski RJ. Basic pharmacology of esmolol. *American Journal of Cardiology* 1985; 56: 3F-13F.
5. Lowenthal DT, Porter RS, Saris SD, Bies CM, Slegowski MB, Staudacher A. Clinical pharmacology, pharmacodynamics and interactions with esmolol. *American Journal of Cardiology* 1985; 56: 14F-18F.
6. Sheppard S, Eagle CJ, Strunin L. A bolus dose of esmolol attenuates tachycardia and hypertension after tracheal intubation. *Canadian Journal of Anaesthesia* 1990; 37: 202-205.
7. Girard D, Shulman BJ, Thys DM, Mindich BP, Mikula SK, Kaplan JA. The safety and efficacy of esmolol during myocardial revascularization. *Anesthesiology* 1986; 65: 157-164.
8. Millar DR, Martineau RJ. Bolus administration of esmolol for the treatment of intraoperative myocardial ischaemia. *Canadian Journal of Anaesthesia* 1989; 36: 593-597.
9. Zakowski M, Kaufman B, Berguson P, Tissot M, Yarmush L, Turndorf H. Esmolol use during resection of pheochromocytoma: report of three cases. *Anesthesiology* 1989; 70: 875-877.
10. Platia EV, Michelson EL, Porterfield JK, Das G. Esmolol versus verapamil in the acute treatment of atrial fibrillation or atrial flutter. *American Journal of Cardiology* 1989; 63: 925-929.
11. Wallis DE, Pope C, Littman WJ, Scanlon PJ. Safety and efficacy of esmolol for unstable angina pectoris. *American Journal of Cardiology* 1988; 62: 1033-1037.
12. Wheat MW. Acute dissecting aneurysms of the aorta: diagnosis and treatment-1979. *American Heart Journal* 1980; 99: 373-386.
13. Roy WL, Edelist G, Gilbert B. Myocardial ischemia during non-surgical procedures in patients with coronary-artery disease. *Anesthesiology* 1979; 51: 393-397.
14. Gray RJ, Bateman TM, Czer LSC, Conklin C, Matloff JM. Comparison of esmolol and nitroprusside for acute post-cardiac surgical hypertension. *American Journal of Cardiology* 1987; 59: 887-891.
15. Cruise CJ, Skrobik Y, Webster RE, Marquez-Julio A, David TE. Intravenous labetalol versus sodium nitroprusside for treatment of hypertension postcoronary bypass surgery. *Anesthesiology* 1989; 71: 835-839.

THE PNEUPAC HYPERBARIC VARIANT HB: A VENTILATOR SUITABLE FOR USE WITHIN A ONE-MAN HYPERBARIC CHAMBER

M. J. SPITTAL, S. J. HUNTER AND L. JONES

SUMMARY

We describe the performance of the pneuPAC hyperbaric variant HB, a ventilator designed for use in a one-man hyperbaric chamber. The ventilator delivered minute volumes of 11–23 litre at 1 atm abs to 7.6–16 litre at 2.5 atm abs. The delivered minute volume may be controlled easily from outside the chamber by manipulation of the ventilator rate, 11.5–31 b.p.m.

KEY WORDS

Equipment: ventilators. Hyperbaria: ventilation.

The pneuPAC range of ventilators has become accepted widely for both resuscitation (Models 1, 2 & 3) and anaesthesia (Model 4). The ventilators work on the moving part, pneumatic logic principle; they are time-cycled, constant flow generators capable of delivering a preset tidal volume irrespective of the patient's airway resistance or lung compliance [1]. However, when a standard pneuPAC ventilator was used in a hyperbaric chamber, the tidal volume decreased exponentially and the frequency increased linearly as the pressure increased until a point was reached at which the performance was no longer adequate [2], because the delivered flow rate and time pulses decreased under the influence of increasing ambient pressure. The most significant reduction in tidal volume occurred when the pressure increased from 1 to 2 atm abs.

The pneuPAC variant HB has been designed specifically for one-man hyperbaric chambers to permit the ventilator to be controlled from outside the chamber.

MATERIALS AND METHODS

The pneuPAC hyperbaric variant HB (fig. 1) comprises a standard pneuPAC Model 2 control

module, a high pressure regulator and relay valve assembly, a chamber module and the standard pneuPAC patient valve.

The pneuPAC control module is driven by a 400-kPa oxygen supply (fig. 2). It has a single control which governs inspiratory time. Expiratory time is not operator adjustable, but varies with inspiratory time [1] to produce I:E ratios of 1:5–1:1.6 and frequencies of 11.5–31 b.p.m. Ventilator rate is depicted on the casing of the control module. Hence the control module generates a breathing pattern, the purpose of which is to provide operator controlled, intermittent switching of the relay valve.

The high pressure regulator reduces cylinder pressure to 6 atm abs, this being 300 kPa greater than the maximum working hyperbaric chamber pressure. The pneumatic relay valve intermittently exposes the chamber module to this 600-kPa oxygen source in the breathing pattern dictated by the control module. Oxygen used to ventilate the patient's lungs is provided entirely from the 600-kPa source.

The chamber module contains a second reducing valve referenced to the ambient chamber pressure; its output is 300 kPa plus ambient chamber pressure, hence the need for a 6-atm abs, oxygen source if the maximum working chamber pressure is 3 atm abs. A factory preset needle valve is incorporated in the module and acts as a flow limiter. There is a constant pressure differential across the valve of 300 kPa (300 kPa plus ambient chamber pressure on one side, ambient chamber pressure on the other) and it is

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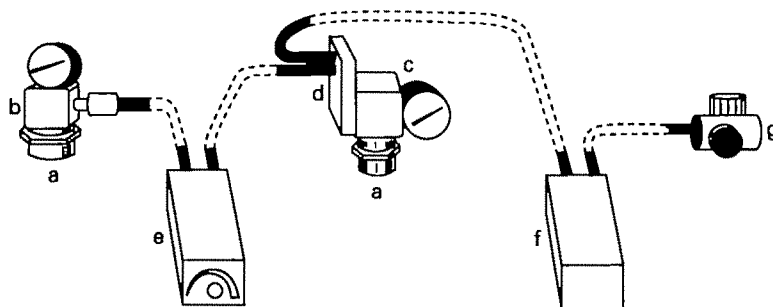


FIG. 1. The pneuPAC hyperbaric variant HB. a = Size G oxygen cylinder (3400 litre); b = pneuPAC reducing valve; c = pneuPAC high pressure reducing valve; d = relay valve; e = pneuPAC Model 2 control module; f = chamber module; g = pneuPAC patient valve.

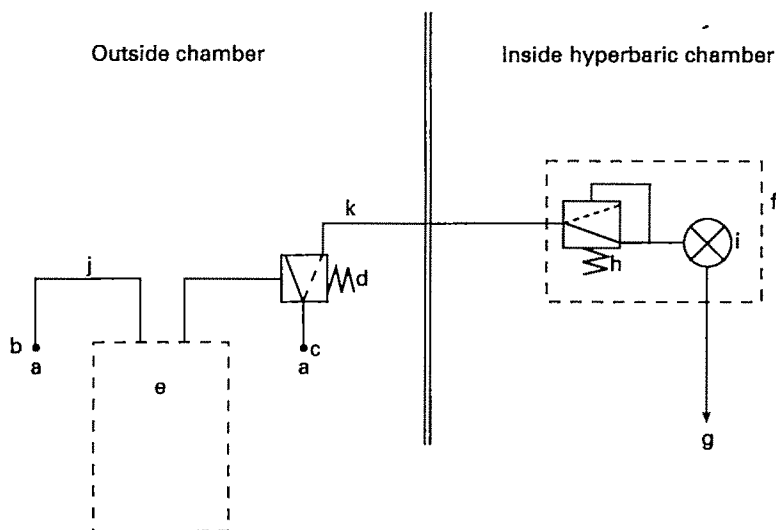


FIG. 2. The pneuPAC hyperbaric variant HB. Principle of operation. a = Size G oxygen cylinder (3400 litre); b = pneuPAC reducing valve; c = pneuPAC high pressure reducing valve; d = relay valve; e = pneuPAC Model 2 control module; f = chamber module; g = pneuPAC patient valve; h = variable output reducing valve; i = flow limiter (needle valve); j = oxygen at 400 kPa; k = oxygen at 600 kPa.

set to allow a flow of $60 \text{ litre min}^{-1}$ at an ambient pressure of 1 atm abs.

Using the Vickers one-man hyperbaric chamber at Princess Alexandra Hospital, we assessed the ventilator through the clinically useful ambient pressure range of 1–2.5 atm abs. Tidal volumes were measured using a Wright's respirometer and

a Medishield calibrated displacement lung ventilation performance tester ($20 \text{ cm H}_2\text{O litre}^{-1}$ compliance) connected in series to the patient valve. Three sets of measurements were made, at pressures of 1, 1.5, 2 and 2.5 atm abs during both the compression and decompression phases; thus there were six measurements of delivered tidal

volume at each pressure. Each measurement represented the mean of three estimations. Ventilator rate was noted also.

RESULTS

Oxygen was used as this is the only gas used clinically in our practice. The minute volumes delivered decreased by 30% as the ambient pressure increased from 1 to 2.5 atm abs (fig. 3).

There was a good correlation between the tidal

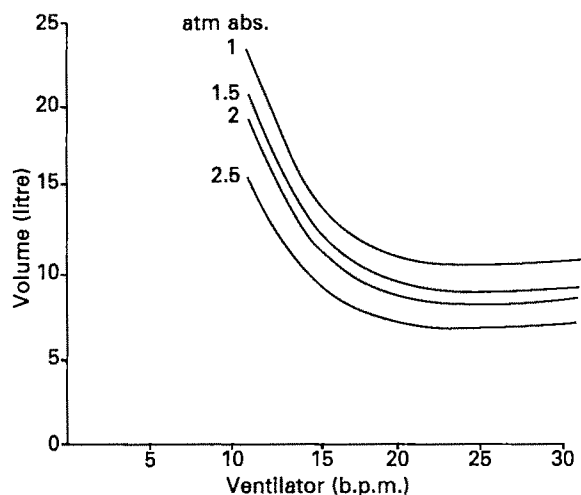


FIG. 3. Comparison of minute volumes delivered (Volume) at different ventilator rate settings with changes in ambient pressure.

volumes measured by the Wright respirometer and the lung ventilation performance tester (table I).

DISCUSSION

The Wright respirometer is prone to under-reading at low tidal volumes and over-reading at high tidal volumes [3], and may be affected by variations in gas density or viscosity. Fortunately, the calibrated displacement lung ventilation performance tester is less likely to be susceptible to these errors and the coefficients of regression and correlation between the two types of apparatus (table I), at the modest volumes and pressures used, support the use of the Wright respirometer alone for monitoring ventilation in clinical practice.

It may be seen from figure 3 that minute volume decreased by 30% as ambient pressure increased from 1 to 2.5 atm abs. This is caused by the characteristics of the flow limiting needle valve in the chamber module. Although the pressure differential across the needle valve is constant, flow through the valve is inversely proportional to the square root of gas density [4]; hence flow decreased with increasing oxygen density as the chamber was pressurized.

Several centres in the U.K. are equipped with one-man hyperbaric chambers which may be used for treatment of severe carbon monoxide poisoning and anaerobic infections. The neuro-pathological lesions of patients who die within hours or days of severe carbon monoxide poisoning include cerebral oedema and necrosis of the globus pallidus and substantia nigra [5].

TABLE I. Mean (SD) tidal volumes measured using lung ventilation performance tester (LVPT) and Wright respirometer (WR) at 1, 1.5, 2 and 2.5 atm abs. b = Regression coefficient; r = correlation coefficient

	PneuPAC control module rate (b.p.m.)					b	r
	31	24	20	17	14		
1 atm abs							
LVPT (ml)	350 (7.1)	470 (18.1)	590 (16.3)	700 (22.3)	850 (25.1)	1.02	0.99
WR (ml)	330 (12.9)	460 (10.1)	590 (14.1)	680 (26.2)	930 (29.4)		
1.5 atm abs							
LVPT (ml)	280 (10.1)	400 (17.2)	530 (12.3)	640 (17.1)	810 (23.3)	1.05	0.99
WR (ml)	270 (6.7)	400 (12.5)	530 (10.4)	640 (24.0)	920 (37.0)		
2 atm abs							
LVPT (ml)	250 (12.7)	400 (9.6)	530 (12.6)	600 (10.3)	830 (27.1)	1.00	1.00
WR (ml)	240 (11.4)	370 (16.3)	490 (14.3)	590 (15.2)	880 (19.6)		
2.5 atm abs							
LVPT (ml)	230 (10.1)	320 (9.6)	400 (14.4)	480 (12.4)	690 (18.1)	0.99	1.0
WR (ml)	230 (9.4)	320 (7.2)	400 (10.7)	440 (14.7)	700 (20.4)		

Hyperbaric oxygen therapy increases the partial pressure of oxygen dissolved in plasma and accelerates dissociation of carbon monoxide haemoglobin, intracellular cytochromes and mitochondria, and also decreases cerebral oedema [6]. Patients typically receive hyperbaric oxygen therapy at pressures of 1.5–2.5 atm abs for up to 90 min. If the performance of a ventilator is degraded by chamber pressurization, hypoventilation ensues, allowing carbon dioxide retention and hence potentially increasing intracranial pressure. It is essential, therefore, to be able to adjust the ventilator to maintain a stable minute volume in response to alterations in chamber ambient pressure. As there is no monitor available for safe measurement of $F_{E_{CO_2}}$ within a hyperbaric chamber, the clinician must therefore base ventilatory requirements on minute volume.

The pneuPAC hyperbaric variant HB is now used routinely in clinical practice. Servicing requirements of the pneuPAC hyperbaric variant

are similar to those of a standard model 2 ventilator; the ventilator therefore requires a manufacturer's inspection every 6 months or 2 years, depending on use.

REFERENCES

1. Adams AP, Henville JD. A new generation of anaesthetic ventilators. The pneuPAC and Penlon A-P. *Anaesthesia* 1977; 32: 34–40.
2. PneuPAC Product Information. *PneuPAC in Hyperbaric Chambers*. PneuPAC Ltd, Crescent Road, Luton, Beds LU2 0AH.
3. Nunn JF, Ezi-Ashi TI. The accuracy of the respirometer and ventigrator. *British Journal of Anaesthesia* 1962; 34: 422–426.
4. Ward CS. *Anaesthetic Equipment*, 2nd Edn. Eastbourne: Baillière Tindall, 1985; 1–14.
5. Fischer B, Jain KK, Braun E, Lehl S. *Handbook of Hyperbaric Oxygen Therapy*. Berlin: Springer-Verlag, 1988; 77–91.
6. Sukoff MH, Ragatz RE. Hyperbaric oxygenation in the treatment of acute cerebral oedema. *Neurosurgery* 1982; 10: 29–32.

FRESH GAS UTILIZATION OF EIGHT CIRCLE SYSTEMS

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SUMMARY

The fresh gas utilization (FGU) of a semi-closed breathing system is defined as the ratio of the amount of gas reaching the patient's lungs to the total amount of fresh gas flowing into the breathing system. It indicates to what extent a breathing system conserves anaesthetic gases and provides inspired gas concentrations as close as possible to those in the fresh gas, even at low fresh gas flows (FGF). We have measured FGU in eight circle systems used conventionally in Europe: Dräger Cicero, Dräger Sulla 808V with circle system 8 ISO and ventilator Ventilog, Dräger AV1, Ohmeda Modulus II Plus, Gambro Engström Elsa, Siemens Servo Ventilator 900 D with circle system 985, Siemens Ventilator 710 and Megamed 700A with circle system 219. The Tests were performed according to the Draft European Standard "Anaesthetic Workstations and Their Modules". None of the systems tested showed the characteristics of an ideal system which would reach 100% FGU with an FGF less than minute volume. At FGF 3 litre min⁻¹, FGU was: Gambro Engström Elsa 97.8%, Siemens Servo Ventilator 900 D with circle system 96.1%, Dräger Cicero 93.4%, Ohmeda Modulus II Plus 93.1%, Dräger 8 ISO 92.3%, Dräger AV1 87.6%, Megamed 700A 77.0% and Siemens Ventilator 710 74.1%.

KEY WORDS

Equipment: breathing systems, fresh gas utilization.

INTRODUCTION

The fresh gas utilization (FGU) of a semi-closed anaesthesia breathing system may be measured as the ratio of the fresh gas reaching the patient (FGP) to the total amount of fresh gas flowing into

the system (FGF). Ideally, all the gas flowing into the system is delivered to the patient and FGU equals unity when fresh gas flow is less than total minute ventilation. In the least desirable case, fresh gas escapes through the exhaust port without reaching the patient and FGU would thus approximate to zero. There are several reasons for striving for high FGU: economy, avoidance of pollution and obtaining inspired gas concentrations that approach the concentrations in the fresh gas even at lower FGF. Inspired gas concentrations differ from fresh gas concentrations as the latter are diluted with exhaled gas within the breathing system. The difference between concentrations in fresh gas and inspired gas depends on many factors: FGF, ventilation, gas uptake by the patient, absorption of anaesthetics to system components, arrangement of the components of the circle system and leakage.

The interaction of these factors make quantitative theoretical prediction of FGU difficult. FGU tends to become small at high FGF and also with systems in which fresh gas may escape easily through the overflow valve, for example because the latter is close to the fresh gas inlet. When inspiratory and expiratory valves are close to the tracheal tube and the overflow valve is placed immediately distal to the expiratory valve, FGU increases [1].

In a previous study [2], circle systems were tested for optimal removal of carbon dioxide using an artificial lung. A similar circle arrangement was found to be optimal but only during controlled ventilation. Thus FGU may be assessed approximately from knowledge of the system architecture. In most cases, however, FGU has to be measured, but so far there is no

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agreement on how FGU should be defined and measured. A recent proposal for a standard test procedure established by the Comité Européen de Normalisation, the Draft European Standard "Anaesthetic Workstations and Their Modules", dated September 18, 1990 has been used in this study [3]. FGU was measured by adding carbon dioxide as a tracer to the fresh gas. This tracer gas was eliminated in a carbon dioxide absorber placed between the Y-piece and test lung. By measuring the remaining concentration of tracer gas in the gas leaving the overflow valve, FGU was determined.

In this study FGU was measured in eight systems which are used commonly in Europe and which have different circle arrangements: the new Dräger Cicero, the Dräger Sulla with circle system 8 ISO and ventilator Ventilog and the Dräger AV1 (Drägerwerke AG, Lübeck, FRG); the Ohmeda Modulus II Plus (Ohmeda, West Yorkshire, England); the Gambro Engström Elsa (Gambro Engström AB, Bromma, Sweden); the Siemens Servo Ventilator 900 D with circle system 985 and the Siemens Ventilator 710 (Siemens-Elma AB, Solna, Sweden); and the Megamed 700A with circle system 219 (Megamed AG, Cham, Switzerland). The functional design of these circle systems is described in the Appendix.

MATERIALS AND METHODS

The experimental plan is depicted in figure 1. Fresh gas was supplied from a cylinder with a gas mixture of 95% oxygen and 5% carbon dioxide. Before each set of measurements, the inflowing concentration of carbon dioxide was measured using an infra-red gas monitor (Capnomac, Datex, Helsinki, Finland). FGF was set at 1.0, 3.0, 6.0, 8.0 and 10.0 litre min^{-1} using a flowmeter calibrated for oxygen (Drägerwerke AG, Lübeck, FRG). The accuracy of this flowmeter was checked using a bell spirometer (Gould Godart Expirograph, Gould Medical B.V., Bilthoven, The Netherlands) and was found to be within $\pm 10\%$ of the actual reading at all flows. The carbon dioxide absorber in the circle system was filled with silica gel beads (Kieselgel 2-5 mm Art. 7735, E. Merck, Darmstadt, FRG) to remove humidity which could affect gas volume measurement. The resistances and effective gas spaces of a container with these silica gel beads and one with ordinary soda-lime (Drägersorb 800, Drägerwerke AG,

Lübeck, FRG) were measured and found to be comparable: at a dry air flow of 60 litre min^{-1} through the container, the resulting pressure at the inlet port was 0.032 kPa both for soda-lime and silica gel beads.

A second container filled with soda-lime 1 litre (Drägersorb 800) was placed between the Y-piece and the test lung. This absorber was tested and found to eliminate all carbon dioxide reaching the patient. The test lung was a Dräger LS 800 (Drägerwerke AG, Lübeck, FRG) with a cuffed 8.5-mm oral tube (Rüsch AG, Waiblingen, FRG) with the following nominal settings: resistance 0.4 kPa litre $^{-1}$ s, compliance 0.6 litre kPa $^{-1}$, leakage 0 litre s^{-1} . At the scavenging port a reservoir bag (2-litre for FGF 1.0 litre min^{-1} , 5-litre for FGF 3 litre min^{-1} and 15-litre for FGF 6, 8 and 10 litre min^{-1}) was attached via a corrugated hose and filled with exhaust gas. This bag was mounted into a rigid container made from plastic material and allowed to fill without pressure. The container was gastight to the interior of the reservoir bag and to the environment. At a second port of the container the anaesthetic gas scavenging system (AGSS) was connected. This arrangement de-

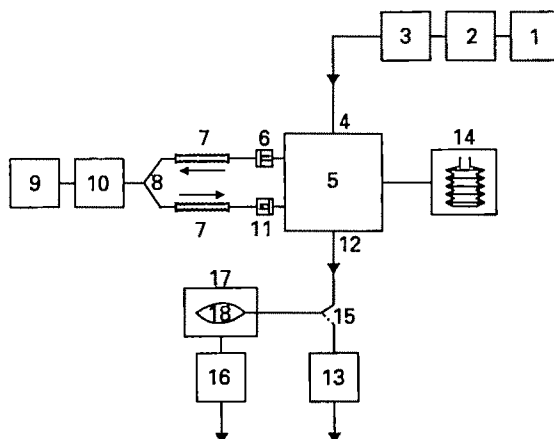


FIG. 1. Experimental plan to measure fresh gas utilization. 1 = Cylinder with premixed gas; 2 = flowmeter for adjusting and measuring the FGF; 3 = measuring device for concentration of carbon dioxide in the fresh gas; 4 = fresh gas inlet port; 5 = circle system in evaluation, with carbon dioxide absorber filled with silica gel beads; 6 = inspiratory unidirectional valve; 7 = breathing tube; 8 = Y-piece; 9 = test lung; 10 = carbon dioxide absorber; 11 = expiratory unidirectional valve; 12 = exhaust port; 13 = measuring device for concentration of carbon dioxide in the exhaust gas; 14 = ventilator; 15 = switch-over valve in position "filling reservoir bag"; 16 = scavenging system; 17 = rigid container; 18 = reservoir bag.

coupled the breathing system from the AGSS, but allowed for pressure influences of the AGSS on the breathing system (by flow and pressure). From the reservoir bag, the well mixed gas was extracted and the mean concentration of carbon dioxide measured using the sideline infra-red gas monitor (Capnomac).

The breathing system was connected to the Y-piece (DAR 600/5086) at the test lung with two breathing tubes (1.0 m in length) (DAR 280/5048, Darex S.P.A., Mirandola, Italy). The measured compliance of each of these tubes was 4.4 ml kPa⁻¹ (measured at a pressure of 2 kPa).

All breathing systems were tested for leakage before measurements were made [4]. At each flow setting, measurements were started after a period of three time constants. A time constant was defined as the circle system volume divided by FGF. The volume of each system was measured including filled absorber, breathing tubes and Y-piece. For the volume measurement, the circuit was sealed completely and a known volume of gas was added. By measuring the increase in pressure, the circuit volume could be calculated. As the soda-lime absorber at the Y-piece became partly consumed during measurements, a small deadspace developed, its size depending on the duration of the measurements. Thus exactly the same time course of measurements was followed for all systems. To compensate for the deadspace, a system volume of 5 litre (which was greater than all the measured volumes) was assumed. For example, FGF 1 litre min⁻¹ required a waiting period of 15 min. To avoid further deadspace in the soda-lime at the Y-piece, fresh soda-lime was used for each change of fresh gas flows. All measurements were performed three times in succession with freshly filled carbon dioxide absorber at each of the five flow settings, resulting in a total of 15 measurements for each system.

The ventilators were adjusted to the following settings: tidal volume 800 ml; ventilatory frequency 10 b.p.m.; I:E ratio 1:2; inspiratory flow at the least value necessary to achieve a tidal volume of 800 ml with the I:E ratio of 1:2; zero PEEP.

As the tidal volumes of Dräger 8 ISO, Ohmeda Modulor II Plus and Siemens Ventilator 710 depend on the fresh gas flow, tidal volume was set using a pneumotachograph (accuracy $\pm 5\%$, Megamed 0577, Megamed AG, Cham, Switzerland) before each measurement. During measurements the pneumotachograph was removed from

the circuit. The tidal volumes of the Dräger Cicero, the Dräger AV1, the Gambro Engström Elsa, the Siemens Servo Ventilator and the Megamed 700A, which are FGF independent, were also measured with this device. A constant deadspace of 50 ml between the Y-piece and the soda-lime canister was maintained.

FGU was calculated using the following equation:

$$FGU = \frac{F_{in} - F_{out}}{F_{in}} \times 100\%$$

where: FGU = fresh gas utilization (%); F_{in} = carbon dioxide concentration measured at the fresh gas inlet (vol %); F_{out} = carbon dioxide concentration measured in the reservoir bag (vol %).

A FGU of 100% implies that all fresh gas reaches the patient.

Because of the difficult working principles of the eight circle systems, it was necessary to choose different settings. In the systems in which the carbon dioxide absorber is placed either in the inspiratory or the expiratory limb (Dräger AV1 and Gambro Engström Elsa) we placed the "dummy" absorber canister in the inspiratory limb. Adjustable pressure limit valves (APL valves) were closed totally or set to the greatest possible value. Only the exceptions in the adjustments or important details are mentioned under the different systems.

Dräger Cicero: To set the inspiratory flow to the smallest value to achieve a tidal volume of 800 ml, the inspiratory pause was set to zero. *Dräger 8 ISO*: The circle system 8 ISO has two inlet ports for fresh gas; both settings were measured. The inlet port between the ventilator port and the carbon dioxide absorber is recommended by the manufacturer. The other inlet port would be between the carbon dioxide absorber and the inspiratory unidirectional valve. The changeover valve (which is a switch at the exhaust port and is used mostly during manual ventilation) was set to the horizontal position. *Dräger AV1*: The standard flowmeters of the ventilator, which are calibrated for a mixture of oxygen and nitrous oxide, were used. *Ohmeda Modulor II Plus*: The inspiratory flow and the I:E ratio cannot be adjusted independently. There is only one knob for setting the inspiratory flow to obtain the required I:E ratio. The inspiratory flow was thus set to obtain an inspiratory pause of 0%. *Gambro Engström Elsa*: This ventilator has an electron-

ically controlled fresh gas mixing system (electronic mass flowmeter). The pump for the implemented anaesthetic agent monitor, which continuously aspirates 200 litre min^{-1} , was switched off. *Siemens Servo Ventilator*: The inspiratory flow cannot be adjusted separately. We set the inspiration time to 25% of the time of one ventilatory cycle (this resulted in a more accurate 1:2 ratio of 1:2 than when selecting the position marked with 33%). The Servo Ventilator has its own fresh gas delivering system which adds fresh gas only during inspiration to the circle system. At FGF values greater than that of minute volume, the ventilator works as a semi-open system. *Siemens Ventilator 710*: The inspiratory flow cannot be adjusted separately. We set the inspiration time to 33% of the time of one ventilatory cycle. *Megamed 700A*: The Megamed circle system has a manually adjustable overflow valve which can be set to three arbitrary positions. Depending on FGF, we chose a position which allowed the reservoir bag to become slightly filled; the tidal volume was then independent of FGF. Position 0.5 was selected for FGF 1 litre min^{-1} , position 1 for 3 litre min^{-1} and position 2 for 6, 8 and 10 litre min^{-1} .

RESULTS

The measured system volumes were: Dräger Cicero 3600 ml, Dräger 8 ISO 1800 ml, Dräger AV1 1700 ml, Ohmeda Modulus II Plus 4900 ml, Gambro Engström Elsa 1800 ml, Siemens Servo Ventilator 2100 ml, Siemens Ventilator 710 1700 ml and Megamed 700A 2300 ml.

Figure 2 depicts FGU of the eight systems in relation to FGF. All systems were less efficient than an ideal system, which would have an FGU of 100% for an FGF less than the ventilatory minute volume. For FGF values greater than that of the minute volume, the ideal FGU is the ratio of minute volume to FGF. In this consideration the system compliance is not taken into account. Table I lists the respective FGU at FGF 3 litre min^{-1} , which is a standard clinical setting. The Dräger 8 ISO improved considerably when the fresh gas inlet was mounted after the soda-lime absorber (table II).

FGU decreased rapidly in all systems when FGF greater than 3 litre min^{-1} were used. Figure 3 shows the FGU of the Dräger Cicero ventilator at different tidal volumes (400 ml, 800 ml and 1200 ml) and the same ventilatory frequency

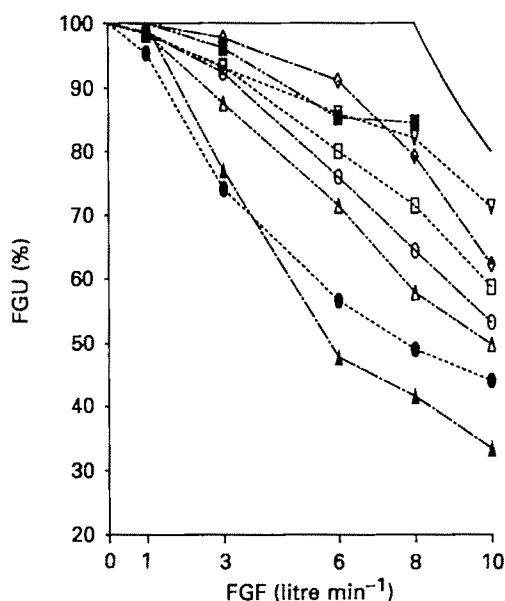


FIG. 2. Fresh gas utilization (FGU) for the anaesthesia breathing systems as a function of fresh gas flow (FGF). $\square$ = Dräger Cicero; $\circ$ = Dräger 8 ISO; $\triangle$ = Dräger AV1; ∇ = Ohmeda Modulus II Plus; $\diamond$ = Gambro Engström Elsa; $\blacksquare$ = Siemens Servo Ventilator; $\bullet$ = Siemens Ventilator 710; $\blacktriangle$ = Megamed 700A; — = ideal.

TABLE I. Fresh gas utilization (FGU) at a fresh gas flow of 3 litre min^{-1} (mean (SEM))

Circle system	FGU (%)
Dräger Cicero	93.4 (0.31)
Dräger 8 ISO	92.3 (0.26)
Dräger AV1	87.6 (0.33)
Ohmeda Modulus II Plus	93.1 (0.50)
Gambro Engström Elsa	97.8 (0.07)
Siemens Servo Ventilator	96.1 (0.35)
Siemens Ventilator 710	74.1 (0.62)
Megamed 700A	77.0 (0.56)

TABLE II. Fresh gas utilization (FGU) in the Dräger 8 ISO circle system with the gas inlet positioned before or after the soda-lime canister

FGF (litre min^{-1})	FGU (%)	
	Inlet before absorber	Inlet after absorber
1	98.7	100
3	92.3	97.9
6	76.0	84.9
8	64.5	75.0
10	53.3	57.7

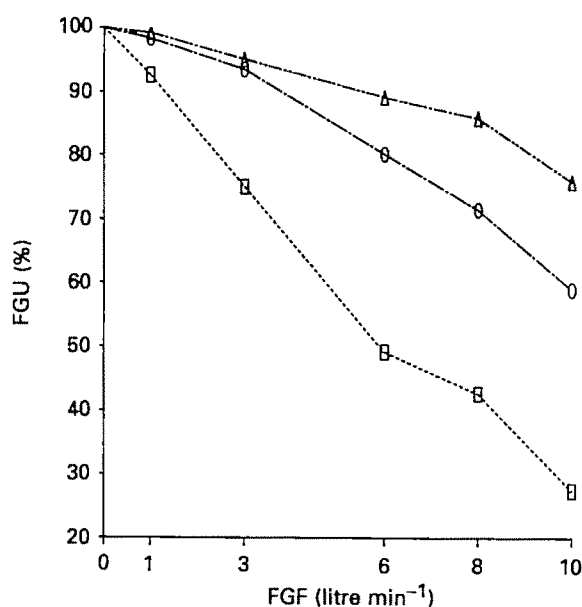


FIG. 3. Fresh gas utilization (FGU) for the circle system Dräger "Cicero" at tidal volumes 400 ml (□), 800 ml (○) and 1200 ml (△), and at a ventilatory frequency of 10 b.p.m.

(10 b.p.m.). At each FGF, FGU increased when the minute volume increased, this effect becoming more evident at greater FGF.

DISCUSSION

At small FGF which would be used clinically in a low-flow anaesthesia technique, all systems approached almost 100% FGU. At greater FGF there was a marked difference between the systems (fig. 2).

The Siemens Servo Ventilator differs from all other circle system. The fresh gas is not flowing continuously, but only during inspiration into the circle system. Thus tidal volume is independent of FGF. For flows greater than minute volume, the ventilator bellows remains in its upper position and the ventilator works as a (semi-open) conventional Servo ventilator without recirculation of expired gases. For this reason, it is not possible to set the minute volume to 8 litre and provide a fresh gas flow of 10 litre min⁻¹.

In an ideal system, all fresh gas would enter the circle during the expiratory phase and be directed to the patient during the phase of inspiration. In systems with a low FGU, such as Megamed and Siemens 710, the fresh gas inlet port is close to the exhaust port which allows fresh gas to escape

without reaching the patient. The Dräger AV1 would have a comparably small FGU if there was not a buffering chamber between the scavenging port and the fresh gas inlet (not shown in figure 4). In the Dräger 8 ISO, fresh gas can escape only during mechanical ventilation through a valve near the bellows, which results in better FGU. In the Ohmeda II Plus, the arrangement is similar but the absorber is placed between the fresh gas inlet port and the overflow valve in the ventilator and this improves FGU. In the Engström ELSA, the fresh gas inlet port is separated from the overflow valve by the expiratory valve or in the inspiratory limb by the soda-lime absorber, both resulting in long pathways for the fresh gas and thus in high FGU values. The importance of separating the fresh gas inlet from the exhaust port is evident in the Dräger 8 ISO: if the fresh gas inlet is mounted after the soda-lime canister (which is an option), FGU improves considerably. This position would also have the advantage that the volatile anaesthetic of the fresh gas is not absorbed by the soda-lime. The Cicero has many electronically controlled valves which should result in optimized FGU values; however, the performance of the system is slightly suboptimal because of the compact construction of the circle resulting in short pathways for the gases.

The described standard proposal test procedure appears to be simple, but this investigation has shown that attention to detail is important. System arrangement, system leaks, inflowing concentration of carbon dioxide, compliance of the tubing, minute volume, soda-lime and the equilibration period for each measurement are important variables. The system arrangement may be important as it may affect resistance to gas flow. Gas leaks inevitably lead to inaccurately great FGU. For this reason, the standard requires a leakage smaller than 50 ml min⁻¹. All systems used in this study fulfilled this criterion as was shown in a separate study [4]. Another cause of gas loss is the carbon dioxide absorbed; thus the standard proposal prescribes a defined inflowing gas concentration of carbon dioxide 6 vol%; in this study, only 5% was available. Compliance of the tubing may influence FGU as well. When highly compliant tubes are used, part of the tidal volume is lost in tube expansion. According to the draft in this study, the same breathing tubes were used for all systems. Ventilation is a further important factor: the greater the minute volume, the greater is FGU. In this study, tidal volume

was measured because in some ventilators tidal volume depends on FGF. In the Cicero, AV1, Gambro Engström Elsa and Megamed, the tidal volume is independent of the amount of inflowing gas. This allows for constant tidal volumes despite changes in FGF. "Alveolar" ventilation may be reduced by deadspace which develops when part of the soda-lime is used up. In this study, soda-lime was changed before each measurement. For the same FGF, the same time constant had to be assumed for all systems, and thus it is assumed that the increasing deadspace in the soda-lime influenced the results to the same (small) extent for all systems.

In an earlier publication, Eger and Ethans investigated the effects of system arrangement on the elimination of alveolar gas [2]. They found that the FGU of various circle arrangements varied greatly, depending on whether ventilation was spontaneous or controlled. Furthermore, an impact of the breathing pattern was important. These factors could not be tested in the present study.

APPENDIX

DESCRIPTION OF THE CIRCLE SYSTEMS

(fig. 4)

Dräger Cicero

The tidal volume is independent of fresh gas inflow. During inspiration, valve 12 is closed and fresh gas is directed into the reservoir bag (6). The ventilator (8) consists of a horizontally positioned piston which is driven electromechanically. The overflow valve (9) is closed during inspiration. All valves (except the inspiratory valve (1) and expiratory valve (2), which are passive ceramic disc valves) are controlled electropneumatically.

Dräger 8 ISO

The tidal volume is dependent on fresh gas inflow. The ventilator (8) consists of a pneumatically controlled hanging bellows. The overflow valve (9) is placed at the ventilator Ventilog and is closed during inspiration. The mechanically adjustable PEEP-valve (7) is placed at the ventilator Ventilog. The valves (except inspiratory valve (1) and expiratory valve (2), which are passive ceramic disc valves) are controlled pneumatically. The exhaust port for mechanical ventilation is at the ventilator Ventilog.

Dräger AV1

The tidal volume is independent of fresh gas inflow. Valve 12 and the PEEP valve (7) are built together. During inspiration, this unit is closed and fresh gas flow is directed

into the reservoir bag (6). The ventilator (8) consists of a pneumatically controlled hanging bellows. The overflow valve (9) is closed during inspiration. All valves (except inspiratory valve (1), expiratory valve (2) and both valves 13, which are passive ceramic disc valves) are electropneumatically controlled. Valve 13 between the ventilator (8) and the reservoir bag (6) is necessary to direct the gas to the patient during inspiration. Valve 13 between the reservoir bag (6) and the fresh gas inlet port (3) is necessary for manual ventilation with the reservoir bag.

Ohmeda Modulus II Plus

The tidal volume is dependent on fresh gas inflow. The ventilator (8) consists of a pneumatically controlled standing bellows. The overflow valve (9) is closed by the driving pressure of the bellow during the inspiration. PEEP cannot be set. The inspiratory valve (1) and expiratory valve (2) are passive disc valves.

Gambro Engström Elsa

The tidal volume is independent of fresh gas inflow. The ventilator (8) consists of a pneumatically controlled reservoir bag (bag-in-bottle principle). The inspiratory and expiratory flows are measured by differential pneumotachographs. The fresh gas is given continuously into the circle system. The inspiration lasts until the desired tidal volume (measured by the inspiratory flowmeter) has been delivered. All valves (except the inspiratory valve (1) and expiratory valve (2), which are passive rubber disc valves) are controlled electropneumatically.

Siemens Servo Ventilator

The tidal volume is independent of fresh gas inflow, provided minute volume is greater than FGF. The ventilator (8) consists of a pneumatically controlled standing bellows. The necessary amount of fresh gas is computed and delivered into the circle system only during inspiration. The bellows position is measured optically. The overflow valve (9) is closed during inspiration. The valves (except the inspiratory valve (1), which is a passive disc valve) are controlled electropneumatically.

Siemens Ventilator 710

The tidal volume is dependent on fresh gas inflow. The ventilator (8) consists of a pneumatically controlled reservoir bag (bag-in-bottle principle). Valve 12 and the PEEP valve (7) are built together. The overflow valve (9) is closed during inspiration. This circle system has two inspiratory and two expiratory valves, which is functionally not necessary. The valves (except inspiratory valve (1) and both valves 13, which are passive disc valves) are controlled electropneumatically.

Megamed 700A

The tidal volume is independent of fresh gas inflow. The inspiratory pressure closes the expiratory valve (2) pneumatically during inspiration, otherwise the reservoir bag (6) would be ventilated. The passive unidirectional valve 13 is necessary to direct gas to the patient during inspiration. This valve is bypassed in the manual mode. The fresh gas flows continuously into the reservoir bag (6). The overflow valve (9) is adjustable manually.

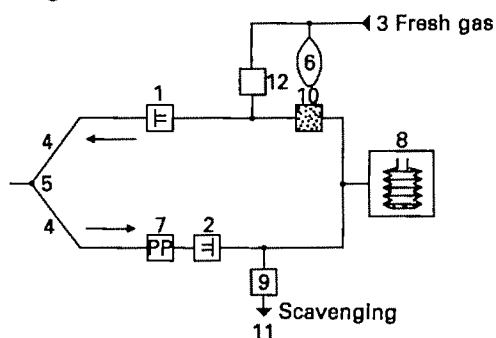
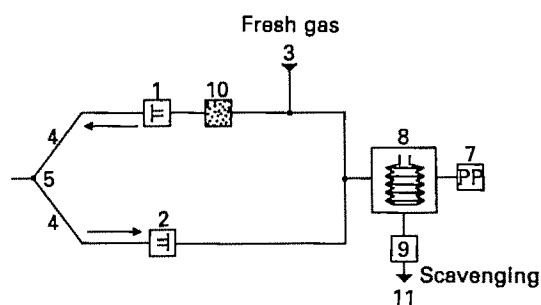
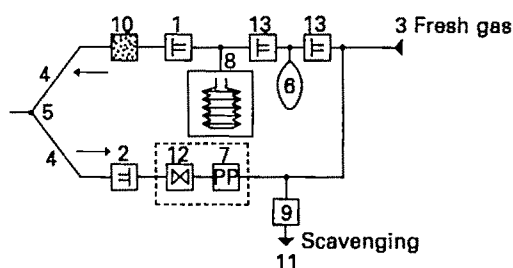
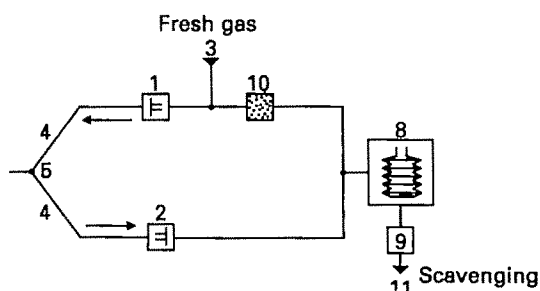
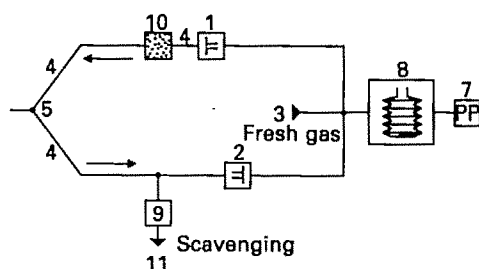
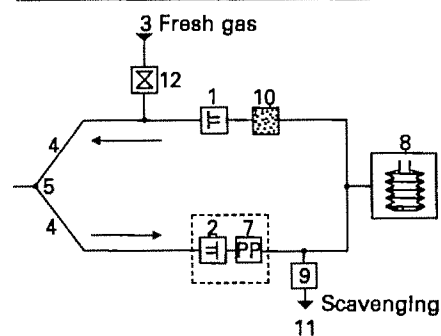
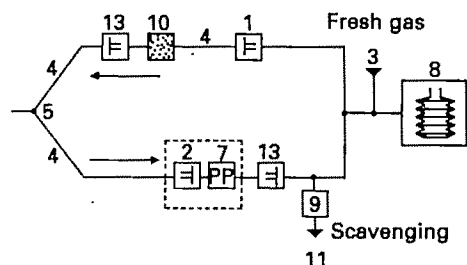
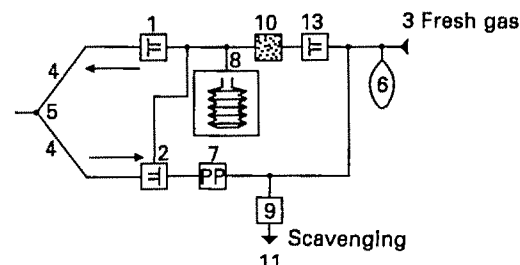
Dräger "Cicero" IPPVDräger "8 ISO" IPPVDräger "AV1" IPPVOhmeda "Modulus II Plus" IPPVGambro Engström "ELSA" IPPVSiemens "Servo Ventilator" IPPVSiemens "Ventilator 710" IPPVMegamed "700A" IPPV

FIG. 4. For legend see facing page.

FIG. 4. Simplified schematic diagram of the different circle systems. 1 = Inspiratory valve; 2 = expiratory valve; 3 = fresh gas inlet port; 4 = breathing tube; 5 = Y-piece; 6 = reservoir bag; 7 = PEEP valve; 8 = ventilator; 9 = overflow valve; 10 = carbon dioxide absorber; 11 = scavenging port; 12 = valve; 13 = unidirectional valve.

REFERENCES

1. Harper M, Eger EI. A comparison of the efficiency of three anesthesia circle systems. *Anesthesia and Analgesia* 1976; 55: 724-729.
2. Eger EI, Ethans CT. The effects of inflow, overflow and valve placement on economy of the circle system. *Anesthesiology* 1968; 29: 93-100.
3. Comité Européen de Normalisation. CEN/TC 215/WG1 N36: *Anesthetic Workstations and Their Modules*, Version 0.32. September 18, 1990.
4. Leuenberger M, Feigenwinter P, Zbinden AM. The gas leakage of six anaesthesia circle systems. *European Journal of Anaesthesiology* 1991; (in press).

CORRESPONDENCE

INHALATION INDUCTION OF ANAESTHESIA WITH ISOFLURANE IN CHILDREN

Sir,—The article concerning the incidence of respiratory complications and hypoxic episodes during inhalation induction with isoflurane in children [1], raises several interesting points.

The authors compared the incidences of three respiratory complications: coughing, breath-holding and laryngospasm during induction of anaesthesia; unfortunately, these complications were not clearly defined. Were they severe enough to be clinically significant, and was intervention (100% oxygen, neuromuscular blocking drugs, tracheal intubation) required at any time? Clearly, all three may vary from mild to complete airway obstruction.

Warde, Nagi and Raftery [1] also presented the results of minimum arterial oxygen saturation (minimum Sp_{O_2}) during induction as incidence within the following ranges: < 71, 71–80, 81–90 and 91–100%. The majority of the children were within the uppermost range. Why were these ranges chosen; could the range 91–100% be further subdivided? Other investigators have used widely differing ranges: Sampaio and colleagues [2] used the ranges < 95% and 95–100% for minimum Sp_{O_2} to compare airway complications, and Phillips, Brimacombe and Simpson [3] used an uppermost range of $\geq 85\%$ as part of a scoring system, but also presented the raw data for the minimum Sp_{O_2} during induction.

At what point does oxygen desaturation become clinically significant? Motoyama and Glazener [4] investigated hypoxia in a group of children after general anaesthesia: 43% developed an Sp_{O_2} of $\leq 91\%$ in the early postoperative period. These authors stated that (assuming a normal acid-base balance and haemoglobin-oxygen affinity) an Sp_{O_2} of < 91% corresponds to a Pa_{O_2} of < 8.0 kPa, which is the value at which the hypoxic ventilatory response becomes evident in awake adult humans. Two children in their study developed an Sp_{O_2} in the range 70–74%. Neither developed cyanosis, bradycardia or increased ventilation; one child was “lightly snoring”, the other did not have any evidence of upper airway obstruction.

Finally, which pulse oximeter was used during the study by Warde, Nagi and Raftery [1]? Two recent articles [5, 6] have reviewed potential errors in pulse oximetry. I would suggest that errors in measurement during an investigation might be sufficient to alter the incidences of minimum Sp_{O_2} values recorded.

Respiratory complications leading to “severe” obstruction result rapidly in oxygen desaturation in children, and pulse oximetry rightly has come to be regarded as essential monitoring during anaesthesia. The relationship between oxygen saturation and “minor” respiratory complications is less clear, and oximetry perhaps is less useful if it distracts the anaesthetist from assessing and managing the airway. Potential errors and significance of pulse oximetry during induction of anaesthesia must also be considered carefully both in clinical practice and in experimental study.

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REFERENCES

1. Warde D, Nagi H, Raftery S. Respiratory complications and hypoxic episodes during inhalation induction with isoflurane in children. *British Journal of Anaesthesia* 1991; 66: 327–330.
2. Sampaio M, Crean P, Keilty S, Black G. Changes in oxygen saturation during inhalation induction of anaesthesia in children. *British Journal of Anaesthesia* 1989; 62: 199–201.
3. Phillips A, Brimacombe J, Simpson D. Anaesthetic induction with isoflurane or halothane. *Anaesthesia* 1988; 43: 927–929.
4. Motoyama E, Glazener C. Hypoxemia after general anaesthesia in children. *Anesthesia and Analgesia* 1986; 65: 267–272.
5. Ralston A, Webb R, Runciman W. Potential errors in pulse oximetry. I. Pulse oximeter evaluation. *Anaesthesia* 1991; 46: 202–206.
6. Webb R, Ralston A, Runciman W. Potential errors in pulse oximetry. II. Effects of changes in saturation and signal quality. *Anaesthesia* 1991; 46: 207–212.

Sir,—Thank you for the opportunity of replying to the letter received from Dr Lewis. Respiratory complications described by us were defined as follows: coughing = any coughing whatsoever from commencement to completion of induction; breath-holding = periods of apnoea during induction exceeding 20 s approximately; laryngospasm = presence during inspiration of a typical “crowing” sound accompanied by the hallmarks of respiratory obstruction in the case of partial spasm, occasionally progressing to absence of sound accompanied by the same clinical signs when spasm was complete (as defined by Patrick [1]). The clinical significance of each of these taken in isolation is not easy to establish. However, the fact that trough Sp_{O_2} during induction was less in the 30 children who developed one or more of these complications than in the 45 who did not, leads us to believe that they were important. Six children, all of whom had respiratory complications, required one or more interventions referred to by Dr Lewis. Three in group A (two with persistent coughing and one with laryngospasm) were given 100% oxygen, while three in group B (three of the four in this group who developed laryngospasm) required the same intervention. One of this latter trio underwent tracheal intubation without use of a neuromuscular blocking drug when Sp_{O_2} decreased to 54%. No child in group C required any alteration to the planned induction technique.

Regarding the Sp_{O_2} ranges used, these were chosen in an attempt to reduce the risk of errors in measurement. We consider that to subdivide the range 91–100% would increase the potential risk for such errors. The oximeter used in all cases was the Critikon Oxyshuttle. We have been happy with its performance for some 3 years and would point out that the trough Sp_{O_2} readings obtained with it in group A children in

the present study were similar to those in group NI children in an earlier paper on isoflurane induction in children published by two of us [2].

We agree with Dr Lewis's opinion that oximetry becomes less useful if it distracts the anaesthetist from assessing and managing the airway, but suggest that this is much less likely to occur if an induction technique with a low incidence of respiratory complications and consequent desaturations (such as that used in our group C children) is used.

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REFERENCES

1. Patrick ME. Airway manipulations. In: Taylor TH, Major E, eds. *Hazards and Complications of Anaesthesia*. Edinburgh: Churchill Livingstone, 1987; 330.
2. Raftery S, Warde D. Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone. *British Journal of Anaesthesia* 1990; 64: 167-169.

UNEXPECTED, DIFFICULT LARYNGOSCOPY

Sir,—Williams, Carli and Cormack [1] have misread the paper by Doré and myself [2], and have drawn some erroneous conclusions. In several places they maintain that the incidence of difficult laryngoscopy was 1 in 300 in our study, the incidence of grade 3 + 4 difficult laryngoscopy [3] was 1 in 292, that the anaesthetist failed to see the cords only once in 292 patients, and that he had an incidence of grade 3 laryngoscopy of one in 292 patients.

We reported on 19 patients "in whom tracheal intubation proved particularly difficult", that is, those who had "more severe degrees of difficulty" at intubation, associated with difficulty at laryngoscopy "such that the anaesthetist could only see the epiglottis (sometimes not even that)". Six of these patients had cervical arthritis, and the overall prevalence of this particularly difficult intubation was 0.5%.

It is inappropriate to exclude patients with neck pathology when quoting the incidence of intubation difficulty. None of our 14 control patients had angle B (V21, our measurement of atlanto-occipital extension) less than 115°, while only three of our difficult intubation patients had a measurement of more than 115° for this angle. Wilson and colleagues [4] found that 46% of their difficult laryngoscopy patients had a clinically appreciable reduction of atlanto-occipital extension.

The Cormack and Lehane grading of difficult laryngoscopy had not been described when our study began, nor did we purport to include all those patients in whom the larynx could not be exposed at laryngoscopy. We did not count those patients whose difficulty of intubation was "inconsequential", but adopted "the more stringent criteria", "admitting only those patients with more severe degrees of difficulty". Wilson and colleagues [4], and now Williams and colleagues [1], giving the same reason, both point out that the incidence of difficult tracheal intubation should be less than the incidence of difficult laryngoscopy.

For these reasons, Williams and colleagues cannot take the results of our study to "obviate some of [their] reservations" that the "original estimate of Grade 3 frequency [at] 1 in 2000... may be too low".

Wilson and colleagues [4] found the incidence of Cormack and Lehane grade 3 (when laryngeal pressure was applied) was 5.4% in a retrospective series (they suggest eagerness in reporting or a lower proportion of experienced anaesthetists), and 1.3% in a prospective series; their incidence of grade 4 was 0.5% and 0.3% in the retrospective and prospective series, respectively. Of course the frequency with which these grades occurs varies from one group of 1000 patients to the next, but my unpublished experience leads me to support the figures reported by Wilson and colleagues.

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REFERENCES

1. Williams KN, Carli F, Cormack RS. Unexpected, difficult laryngoscopy; a prospective survey in routine general surgery. *British Journal of Anaesthesia* 1991; 66: 38-44.
2. Bellhouse CP, Doré C. Criteria for estimating the likelihood of difficulty of endotracheal intubation with the Macintosh laryngoscope. *Anaesthesia and Intensive Care* 1988; 16: 329-337.
3. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; 39: 1105-1111.
4. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. *British Journal of Anaesthesia* 1988; 61: 211-216.

Sir,—May we comment briefly on the letter from Dr Bellhouse.

Patients with neck pathology. These were excluded from our unexpected difficult intubation group because difficulty in such cases is not *unexpected*, or should not be. In our 1984 study, we stated that if Caesarean section is to be carried out in a patient with neck pathology, such as in Still's disease, a senior anaesthetist must be notified. Two years later, a Confidential Enquiry [1] reported a death in a severely arthritic patient—the registrar had carried out a standard failed intubation drill to the best of his ability, but fatal Mendelson's syndrome occurred. Was he wise to start this case on his own?

Patients without neck pathology. The study by Bellhouse and Doré [2], in which they claimed to be able to predict nearly all difficult intubations is well known, and rightly so. Scurr remarked many years ago that an experienced anaesthetist may know when trouble is brewing, although he may be unable to state the reasons. Unfortunately, it has become clear that, for most of us, this is not true. Despite world-wide efforts to solve this problem, the results have been disappointing—for example, a recent survey [3], using both Mallampati's sign and Wilson's risk-sum method, found that 50% of the difficult cases were missed. Clearly, this strategy is not going to work unless the methods can be improved.

Thus difficulty is easy to predict in arthritic patients and trouble can be forestalled; the problem cases are those which are difficult despite the absence of neck pathology. After subtracting the arthritic patients from the data of Dr Bellhouse, the incidence of unexpected difficulty is 0.3%, as we stated, not 1.3%.

It is perhaps an academic question which of these figures is correct, as the main conclusion is the same from both, namely that junior anaesthetists will have had little or no experience in handling difficult intubations by the time they start doing "full-stomach" cases on their own. It follows that a training

drill which simulates the difficult case is needed. The incidence of failed intubation in obstetrics is quoted widely as 1 in 300; our current figure is 1 in 800, which suggests that the simple expedient of practising the Macintosh method may produce a valuable improvement.

Maternal deaths associated with difficult intubation are bound to raise questions in court about the training of junior staff—those responsible for training could be subpoenaed. An Army commander who sent troops into action undrilled would have some difficult questions to answer!

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REFERENCES

1. DHSS. *Report on Confidential Enquiries into Maternal Deaths in England and Wales in 1979-1981*. London: HMSO, 1986; 86-87.
2. Bellhouse CP, Doré C. Criteria for estimating likelihood of difficulty of endotracheal intubation with the Macintosh laryngoscope. *Anaesthesia and Intensive Care* 1988; 16: 329-337.
3. Oates JDL, MacLeod AD, Oates PD, Pearsall FJ, Howie JC, Murray GD. Comparison of two methods for predicting difficult intubation. *British Journal of Anaesthesia* 1991; 66: 305-309.

DESATURATION DURING TOTAL KNEE REPLACEMENT

Sir,—Since publishing my previous work [1], I have encountered two cases of desaturation in patients, aged 67 and 71 yr, undergoing total knee replacement under general anaesthesia.

Premedication consisted of papaveretum 10 mg with hyoscine 0.2 mg. Anaesthesia was induced with thiopentone 300 mg and tracheal intubation was facilitated by vecuronium 6 mg. The lungs were ventilated mechanically and anaesthesia was maintained with 66% nitrous oxide and 1% enflurane in oxygen. Both patients were in the supine position. The arterial pressure, oxygen saturation and inspired oxygen concentration were monitored non-invasively (Cardiocard, Datex). The oximeter probe was positioned on the ear. Both patients were healthy and non-smokers, and both demonstrated a decrease in saturation, of 3% and 5% respectively, which occurred 1 min after insertion of cement for the femoral components. The episodes of desaturation lasted for 5 and 7 min, respectively, with no accompanying changes in arterial pressure or heart rate. There were no other episodes of desaturation during the procedures. Both patients had a tourniquet around the thigh at pressures of 175-200 mm Hg greater than the systolic arterial pressure. The prostheses used were of the short-stemmed Kinnamax variety.

Desaturation during cemented total knee replacement has been reported [2]. It has been suggested that pulmonary changes were more common with use of the long-stemmed total knee prostheses than with the short-stemmed, because of the relatively large intramedullary cavities and the larger amount of cement required. It is possible that emboli (fat, cement, air or marrow) are forced into the systemic circulation through the intramedullary vessels as the cement sets—a

process that results in increased intramedullary pressures [3]. This may explain the occurrence of systemic emboli despite the use of tourniquets.

As it has been shown that use of an F_{iO_2} of 0.5 significantly reduces the incidence of desaturation in total hip replacement, the same recommendation should apply to total knee replacement.

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REFERENCES

1. Al-Shaikh B. Effect of inspired oxygen concentration on the incidence of desaturation in patients undergoing total hip replacement. *British Journal of Anaesthesia* 1991; 66: 580-582.
2. Byrick RJ, Forbes D, Waddell JP. A monitored cardiovascular collapse during cemented total knee replacement. *Anesthesiology* 1986; 65: 213-216.
3. Kallos T, Enis JE, Gollan F, Davis JH. Intramedullary pressure and pulmonary embolism of femoral medullary contents in dogs during the insertion of bone cement and prosthesis. *Journal of Bone and Joint Surgery* 1974; 56: 1363-1367.

ATRACURIUM AND SUXAMETHONIUM

Sir,—We read with great interest the paper by Donati and colleagues [1] in which the pharmacokinetic and pharmacodynamic components of the change in dose response to atracurium after previous exposure to suxamethonium were elegantly elucidated. The paper adds strong evidence of a significantly increased sensitivity of the neuromuscular junction to non-depolarizing neuromuscular blocking agents after previous exposure to suxamethonium.

We would like to point out a small error (obviously a slip of the pen), which initially caused us some confusion. In the first paragraph of the introduction the sentence "A shift to the right of the dose-response curve to vecuronium [3] has been described with previous exposure to suxamethonium" should read "A shift to the left...".

N. J. FAUVEL
S. A. FELDMAN
London

REFERENCE

1. Donati F, Gill SS, Bevan DR, Ducharme J, Theoret Y, Varin F. Pharmacokinetics and pharmacodynamics of atracurium with and without previous suxamethonium administration. *British Journal of Anaesthesia* 1991; 66: 557-561.

Sir,—Thank you for the opportunity to respond to Drs Fauvel and Feldman, who should be congratulated for their careful reading of our report. They are, of course, correct in suggesting that we should have said "A shift to the left...". We hope they will accept our apologies for this unfortunate "slip of the pen...".

F. DONATI
Montreal

TRAINING IN FIBROPTIC LARYNGOSCOPY

Sir,—I read with interest the editorial on "Training in Fibreoptic Laryngoscopy" [1]. I propose a solution to some of the ethical and practical problems which were outlined so thoroughly by Dr Vaughan.

For the past year, we have conducted a joint diagnostic bronchoscopy list with physicians. Bronchoscopies are performed in the presence of a trainee anaesthetist, a senior anaesthetist familiar with fiberoptic techniques and a physician. Two main techniques are used; both are performed through the mouth and under sedation after preparation of the airway with local anaesthetic spray and a cricothyroid puncture. The first "unaided" technique involves a standard oral intubation with the fiberoptic bronchoscope with subsequent "railroading" of a tracheal tube into the trachea. The second "aided" technique involves the insertion of a Laryngeal Mask Airway with the patient awake, followed by fiberoptic bronchoscopy through that airway [2]. General anaesthesia and other techniques are used occasionally where indicated on clinical grounds.

This list has advantages to all parties. For the patient the passage of a tracheal tube or laryngeal mask airway permits better oxygenation; the presence of the anaesthetist contributes to better immediate care, the physician gains exposure to airway management methods, and in difficult cases can concentrate on the procedure itself. The advantage to the trainee anaesthetist is that he can learn the basics of fiberoptic bronchoscopy and become familiar with a technique for awake intubation. In addition, the trainee gains exposure to patients with poor respiratory function and may learn something about bronchial anatomy. Finally, this list has allowed us to forge better relationships with our physician colleagues.

J. BRIMACOMBE
Queensland, Australia

REFERENCES

1. Vaughan RS. Training in fiberoptic laryngoscopy. *British Journal of Anaesthesia* 1991; 66: 538-540.
2. Brimacombe J. The Laryngeal Mask Airway—use in awake diagnostic bronchoscopy. *Anaesthesia and Intensive Care* 1991; (in press).

Sir,—We read with interest the recent editorial by Dr R. S. Vaughan [1]. We also are interested in the reasons why British anaesthetists have been so slow in embracing the advances in fiberoptic technology, and we question his statement "the main reason for such delay [in embracing fiberoptic technology] has probably been the cost of each specialized piece of equipment". We have contacted the Chairmen of all Anaesthetic Departments in the South West Thames Region, initially by letter, to ascertain what facilities and training programmes in fiberoptic intubation were available. All non-responders were contacted by telephone. The following questions were asked:

- (1) Does your department have access to a fiberoptic endoscope suitable for intubation purposes. If not why not?
- (2) Are there problems with the care and maintenance of the endoscope?
- (3) Is there a permanent member of staff in your department who is skilled at awake fiberoptic intubation?
- (4) Do you have a formal training programme for junior anaesthetic staff to become skilled in the use of the fibroscope? Does this include training on: (a) a mannekin; (b) anaesthetized patients; (c) awake patients?

tized patients; (c) awake patients?

Of the 14 hospitals in South West Thames through which anaesthetic juniors rotate, 11 possess a fibroscope designed specifically for intubation purposes. All hospitals without a purpose-designed scope stated that lack of funds was the reason they did not have one. No hospital reported problems with the care and maintenance of the equipment. All 11 positive responders reported that they had a permanent member of staff skilled in awake fiberoptic intubation.

Despite the presence of suitable equipment in the majority of hospitals and a member of skilled staff, only five reported that they had established training programmes. In all five institutions, this included teaching in anaesthetized patients; three provided training in awake intubation, whilst two reported that they possessed a mannekin suitable for training purposes. Thus it appears that, in the majority of hospitals in the South West Thames Region, there is both the practical skill and the equipment available for fiberoptic intubation, but a paucity of formal teaching programmes.

The ability safely to secure the airway is fundamental to the practice of anaesthesia. Fiberoptic intubation is an important additional skill to possess, particularly when one is faced with a "difficult airway". It has a high success rate compared with other techniques [2] and, more importantly, has a high degree of patient safety. All anaesthetic trainees should be proficient at awake fiberoptic intubation, as are their American counterparts at the end of their much shorter (3-year) training programme.

R. J. TELFORD
P. R. RAWLE
London

REFERENCES

1. Vaughan RS. Training in fiberoptic laryngoscopy. *British Journal of Anaesthesia* 1991; 66: 538-540.
2. Ovassapian A, Yelich SJ, Dykes MHM, Brunner EE. Fiberoptic nasotracheal intubation—incidence and causes of failure. *Anesthesia and Analgesia* 1983; 62: 692-695.

REPORTING OF DEATHS

Sir,—The report of the tragic death of a 26-yr-old woman [1] prompts me to write to you with a suggestion. This death was not reported to the National Confidential Enquiry into Perioperative Deaths because of some local difficulties in the system which have resisted our attempts at solution. Nevertheless, the management of this patient was exemplary and the report informative; it is unfortunate that the case is omitted from the central audit system. Adverse reactions to drugs should be reported in addition to the Committee on Safety of Medicines through the yellow card system.

Editors of journals associated with our specialty might like to agree informally to encourage reporting by the simple expedient of asking authors of reports submitted for publication to do so, perhaps in their notice or guide to contributors.

J. LUNN
Cardiff

REFERENCE

1. Ewah B, Calder I. Intraoperative death during lumbar discectomy. *British journal of Anaesthesia* 1991; 66: 721-723.

ANTAGONISM OF BENZODIAZEPINE SEDATION WITH FLUMAZENIL

Sir,—As a group of clinicians with considerable experience with the use of flumazenil during anaesthesia, day-case surgery, endoscopy and in the care of the critically ill, it was with concern that we read the paper by Sanders and colleagues [1]. The midazolam–flumazenil (agonist–antagonist) concept has been shown to be safe and cost effective [2–7] and is widely used in day-case surgery and endoscopy. The conclusions drawn by the authors about the usefulness of flumazenil are inappropriate and not supported by their data.

The doses of agonists used in this study exceed those generally accepted and recommended as safe practice [8]. This may be reflected in the large number of patients who were unable to complete the tests. The translation of percentages to non-integer patient numbers in tables II and IV suggests that these patients have been excluded from analysis, introducing a serious bias.

The use of atropine invalidates the vision-dependent tests used in this study. The concentration of flumazenil and the volume given to patients do not agree with the stated doses.

No primary criterion of efficacy was defined in this study. There were multiple hypotheses tested, reflected by more than 200 statistical tests being reported. Several statistically significant results based on chance alone would be expected from so many comparisons.

A stated aim of the study was to assess how easy it is to judge the correct dose of flumazenil. It is therefore surprising that the results of both concentrations of flumazenil are combined, making this aim unattainable.

In the penultimate paragraph the authors state that patients benefit from sleeping. Since the authors could show little effect on sleeping, the conclusion must be doubtful.

Although safety is mentioned in the conclusion, no measure of safety was included in the study. The subjective assessments cannot be regarded as spontaneous adverse reporting as the investigators imply. The introduction of flumazenil into the area of endoscopy and day-case surgery represents a major advance in patient safety. Providing patients are not overdosed with midazolam, early discharge is safe after antagonism with flumazenil if the patient is accompanied.

R. MCCLOY	G. PARK
R. PEARSON	Cambridge
Manchester	D. BELL
J. WHITWAM	Ipswich
R. MILLER	E. GELLER
London	Tel Aviv

REFERENCES

- Sanders LD, Piggott SE, Isaac PA, Okell RW, Roberts B, Rosen M, Robinson JO. Reversal of benzodiazepine sedation with the antagonist flumazenil. *British Journal of Anaesthesia* 1991; 66: 445–453.
- Kirkegaard L, Knudsen L, Jensen S, Kruse A. Benzodiazepine antagonist Ro 15-1788. *Anaesthesia* 1986; 41: 1184–1188.
- Payne-James JJ, Loft DE, Killaspy H, Gorard D, Misiewicz JJ, Silk DBA. Reversal of benzodiazepine induced amnesia after short diagnostic procedures by flumazenil (Anexate). *European Journal of Gastroenterology and Hepatology* 1991; 3: 91–94.
- Pearson RC, McCloy RF, Morris P, Bardhan KD. Midazolam and flumazenil in gastroenterology. *Acta Anaesthesiologica Scandinavica* 1990; (Suppl. 92) 34: 21–24.
- Birch BRP, Anson K, Gelister J, Parker C, Miller RA. The role of midazolam and flumazenil in urology. *Acta Anaesthesiologica Scandinavica* 1990; (Suppl. 92) 34: 25–32.
- Birch BRP, Anson KM, Miller RA. Sedoanalgesia in urology: a safe, cost-effective alternative to general anaesthesia. *British Journal of Urology* 1990; 66: 342–350.
- Andrews PJD, Wright DJ, Lamont MC. Flumazenil in the outpatient. *Anaesthesia* 1990; 45: 445–458.
- Whitwam JG, Al Khudhari D, McCloy RF. Comparison of midazolam and diazepam in doses of comparable potency during gastroscopy. *British Journal of Anaesthesia* 1983; 55: 773–777.

Sir,—The letter of Mr McCloy and colleagues has many points which we will consider in order.

The doses of agonists administered were dictated by the clinical judgement of the endoscopist. The initial doses were 0.07 mg kg⁻¹ for midazolam and 0.15 mg kg⁻¹ for diazepam; this, however, failed to provide an adequate degree of sedation for the procedure, and supplementary doses had to be administered at the request of the endoscopist. The percentages given in tables II and IV were necessary because, for 15 patients, this information was not recorded by the anaesthetist; percentages provided the minimally offensive way to compare between groups.

There are misprints in the stated strengths of the antagonist; the full strength was 0.1 mg ml⁻¹, half strength 0.05 mg ml⁻¹. The figures given in table I for the total doses of flumazenil administered are correct.

The audio task showed the same extent of impairment as the visual tasks, therefore there seems no reason to attribute the degree of impairment of the latter to atropine.

In the psychometric results (table III) all the significant changes are consistent with a depression in performance and most of these have *P* values less than 0.01. There appears no reason to attribute such a result to a multiplicity of tests. As the results from the visual analogues were not as consistent, the very conservative Bonferroni adjustment was used as stated in the text (p. 450).

It is obvious from the doses of the antagonist administered (table I), that it was not at all easy for the clinician to determine the correct dose.

Of the 20 patients in the midazolam–placebo group, six could not be roused for the first test session, compared with one of the 40 patients who received midazolam–flumazenil (p. 451). This demonstrates a significant effect of flumazenil on sleep (*P* = 0.008).

At no point in the article is it implied that subjective assessments were equivalent to or the same as spontaneous adverse reporting. We quite expressly state that subjective effects were recorded on visual analogues (pp. 447, 450).

Mr McCloy and his colleagues assert that the introduction of flumazenil represents a major advance in patient safety, with which we would agree, and that early discharge is safe *if the patient is accompanied* (our italics). This is the point: if the patient is accompanied, potential dangers from undetected impairment are much less likely. Our article demonstrates that these may exist after flumazenil.

L. SANDERS
M. ROSEN
P. ISAAC
Cardiff

PREDICTING DIFFICULT INTUBATION

Sir,—Oates and colleagues [1] reported a useful study, comparing two published methods of predicting difficult intubation, and have added to the considerable recent literature encouraging preoperative attempts to predict difficult intubation as part of a routine to increase patient safety.

The authors acknowledged how important it is to perform the Mallampati test [2] correctly and, because observer 4 was not doing this during the study, subtracted the results for this observer. This gave a sensitivity to the Mallampati test slightly better than that for the Wilson test [3] and specificity and positive predictive value (PPV) slightly less.

After the authors removed the data of observer 4 from their results, nine difficult laryngoscopies (grades 4 and 5) remained. This makes it hard for the reader to obtain sensitivities of "0.40" and "0.50" in table III for the Wilson and Mallampati methods. Presumably this should have been "4/9", and "5/9".

When I reviewed the data presented graphically in figure 3, and subtracted the observer 4 results, I obtained a lower proportion (about 11%) of patients for whom two observers disagreed over scoring when the Mallampati classification was used, than when the Wilson method was used (about 15%).

Previous recommendations have been made that some head extension should be added to the Mallampati technique to improve its accuracy [4, 5], but it is interesting that the single Mallampati predictor gave results comparable to those with the five-point Wilson method, although the Wilson method required five examinations. Although the results were comparable for the Mallampati method with apparently less observer variation (when observer 4 was correctly neglected), the authors preferred the Wilson method. It is significant however, that they declined to recommend it.

The study would have been more valuable if the authors could have analysed their figures further, attempting to discover to what extent adding Mallampati's examination improved the sensitivity, specificity and PPV of the Wilson classification.

The authors repeated our emphasis [5] that it is important for the anaesthetist to try to predict difficult intubation when presented with a patient at risk of regurgitation.

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New South Wales

REFERENCES

1. Oates JDC, Macleod AD, Oates PD, Pearsall FJ, Howie JC, Murray GD. Comparison of two methods for predicting difficult intubation. *British Journal of Anaesthesia* 1991; 66: 305-309.
2. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Warksa B, Fyeiburger D, Liu PL. A clinical sign to predict difficult tracheal intubation: A prospective study. *Canadian Anaesthetists Society Journal* 1985; 32: 429-434.
3. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. *British Journal of Anaesthesia* 1988; 61: 211-216.
4. Samsoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; 42: 487-490.
5. Bellhouse CP, Doré C. Criteria for estimating likelihood of difficulty of endotracheal intubation with the Macintosh laryngoscope. *Anaesthesia and Intensive Care* 1988; 16: 329-337.

Sir,—Thank you for allowing us the opportunity to comment on Dr Bellhouse's letter.

The values for sensitivity, specificity and positive predictive value (PPV) for observers 1-3 in table III were derived from data from a total of 543 patients. Of these, 10 (not nine, as stated in the text) were laryngoscopy grade 4 or 5, with five true positives for Mallampati and four true positives for the Wilson method. We thank Dr Bellhouse for drawing our attention to this error. The values in table III are correct.

The percentages of patients assessed by two observers, excluding observer 4, where the observers disagreed over predicting easy or difficult laryngoscopy were 11.8 (95% CI 6.8-16.8) for Mallampati classification and 15.6 (95% CI 10.1-21.1) for Wilson risk sum.

We did examine the effect of combining the Mallampati classification with the Wilson risk-sum, although this was not reported in our paper. Using the data for observers 1-3, we substituted Mallampati class for jaw movement in the Wilson risk-sum and took a modified risk-sum of 3 or more as a predictor of difficult laryngoscopy (to allow for the effect of the Mallampati class starting at 1). Complete data were available for 517 patients, of whom nine were graded difficult at laryngoscopy. Sensitivity, specificity and PPV were 0.44, 0.85 and 4.9%, respectively. If the Wilson risk score for head and neck movement and Mallampati class were summed, for a modified risk-sum of 3 or more as a predictor, sensitivity, specificity and PPV were 0.44, 0.91 and 8.0%, respectively. We found, therefore, that combining Mallampati with Wilson produced no significant improvement in sensitivity or positive predictive value over the individual tests.

J. D. L. OATES
A. D. MACLEOD
P. D. OATES
F. J. PEARSALL
J. C. HOWIE
G. D. MURRAY
Glasgow

DIPRIVAN INTENSIVE CARE SEDATION IN CHILDREN

Sir,—We have received a number of reports of Diprivan (propofol) use in intensive care sedation of children, a use for which the product is not licensed or tested. Some of these reports have involved the occurrence of adverse neurological events during the recovery phase, ranging from minor twitching to convulsions and have also involved extrapyramidal events such as choreo-athetosis. The majority of children were aged between 6 months and 3 yr and many were being sedated with Diprivan for acute respiratory tract infections.

A common feature of all these cases is that the doses of Diprivan used (between 6 and 17 mg kg⁻¹ h⁻¹) were far greater than those suggested for adults (1-4 mg kg⁻¹ h⁻¹). Very often, accompanying analgesia was not used to avoid respiratory depression and this may have led to these excessive dose requirements.

We are aware that some doctors may wish to use Diprivan in this patient group, but without further clinical data we cannot recommend or support this practice.

ELAINE M. RODGERS
Medical Adviser, ICI Pharmaceuticals
Macclesfield

SYSTOLIC ARTERIAL PRESSURE AS A MONITOR OF DEPTH OF ANAESTHESIA

Sir,—When Robb and colleagues [1] wrote: "The use of clinical signs (SAP in this case) to guide anaesthetic dosage... was the approach adopted by Suppan in his pioneering studies", they gave the impression that Suppan [2] was the first anaesthetist to use arterial pressure as an indicator of adequacy of anaesthesia. However, when halothane was first introduced, several authors recommended using arterial pressure as an index of depth of anaesthesia. I was taught during my residency that, during anaesthesia, the SAP should always be maintained within 20% of baseline.

Maintaining the SAP within these limits throughout anaesthesia and injecting intermittent volumes of liquid enflurane in the expiratory limb of a closed system [3], we have observed that the accumulated volume of enflurane was, on average, only about 50% of predicted, whereas the use of halothane and isoflurane was found to agree with predicted volumes [4–8]. The reasons for these various deviations from Lowe's theory [3] could not be detected in Brazil because there was no means of measuring end-tidal concentrations.

In 1986 at the University of Wales College of Medicine, an exploratory study confirmed the Brazilian findings [9], and during the IVth International Symposium of the Closed and Low Flow Anaesthesia Society, Couto da Silva, Vickers and Mapleson showed a nomogram in which SAP correlated with the depth of anaesthesia. Therefore, the finding of Robb and colleagues [1] confirms that "SAP may be major component of the clinical assessment of the anaesthetic state" [1] observed previously by other authors.

J. M. COUTO DA SILVA
Brasília, Brazil

REFERENCES

- Robb HM, Asbury AJ, Gray WM, Linkens DA. Towards a standardized anaesthetic state using enflurane and morphine. *British Journal of Anaesthesia* 1991; 66: 358–364.
- Suppan P. Feed-back monitoring in anaesthesia. IV: The indirect measurement of arterial pressure and its use for the control of halothane administration. *British Journal of Anaesthesia* 1977; 49: 141–150.
- Lowe HJ. *Dose Regulated Penthrane Anaesthesia*. North Chicago, Ill.: Abbott Laboratories, 1972.
- Silva JMC, Oliveira KGB, Saraiva RA, Pereira, E. O baixo fluxo de gases em pacientes adultos. *Revista Brasileira de Anestesia* 1983; 33: 220.
- Silva JMC, Napolini Filho H, Vieira ZEG, Saraiva RA. Influência da medicação pré-anestésica na DA_{95} do enflurano. *Revista Brasileira de Anestesia* 1985; 35: 267–274.
- Silva JMC, Cunha MAS. Indução da anestesia com enflurano pelo método quantitativo de anestesia. *Revista Brasileira de Anestesia* 1986; 35: 267–274.
- Couto da Silva JM, Carvalho SSS, Vieira ZEG, Saraiva RA. Influência da medicação pré-anestésica na DA_{95} do enflurano. *Revista Brasileira de Anestesia* 1986; 36: 381–390.
- Couto da Silva JM, Murici MS, Freitas EL, Cunha MAS. Indução da anestesia pelo método quantitativo. Estudo comparativo com enflurano, halothano e isoflurano. *Revista Brasileira de Anestesia* 1988; 38: 83–92.
- Couto da Silva JM. Closed system anaesthesia (Ph.D. Thesis). Cardiff: University of Wales College of Medicine, 1990.

Sir,—Thank you for the opportunity to comment on the interesting letter from Professor J. M. Couto da Silva.

We feel that it is particularly important to see the comments in our paper in the context of closed loop automatic control of the anaesthetic process, and our comments about Suppan's work were made in this context. Of course we do recognize that others have used arterial pressure as a method of assessing adequacy of anaesthesia, but not in closed loop control.

Furthermore, the words in our paper were chosen carefully to reinforce the fact that SAP is only one part of the range of clinical signs observed regularly by anaesthetists, and that it should be seen in context. We agree that SAP carries considerable information about adequacy of anaesthesia within the confines of our work where, for example, there were no beta-blockers, antihypertensive drugs or major blood loss.

A. J. ASBURY
Glasgow

PAIN ON I.V. INJECTION

Sir,—We have read with interest the paper of Klement and Arndt [1] entitled "Pain on i.v. injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations." However, this title is misleading, as the authors studied the intensity and time course of pain after injection of saline and glucose solutions of differing osmolalities (0–6 osmol kg^{-1}) or pH (2–13) and not the pain-inducing properties of i.v. anaesthetic agents.

In their study, solutions with osmolalities greater than 1 osmol kg^{-1} and pH either less than 4 or greater than 11 were found to evoke pain after injection into an isolated vein segment. It was observed also that pain intensity increased almost linearly with osmolalities of the test solution—starting at 3.0 osmol kg^{-1} (pain threshold) and ending at 6.0 osmol kg^{-1} (pain tolerance maximum). Based on the above observations, the authors postulate that the major pain stimulus is the osmolar concentration rather than the ionic strength of the solution. This is, however, difficult to reconcile with the fact that propofol in its currently-used soya bean emulsion formulation with an osmolality of 0.280 osmol kg^{-1} , close to that of blood, and a pH of 8 [2] frequently causes more pain on injection [3–6] than thiopentone with a similar osmolality of 0.215 osmol kg^{-1} and a pH of 11. Bretschneider [7], in a study quoted by Klement and Arndt, measured the osmolality of 65 drugs used in anaesthesia, the majority of which (48 compounds) showed an osmolality between 0.113 and 1.0 osmol kg^{-1} . We feel that the choice of the extreme range of osmolalities (1.0–6.0 osmol kg^{-1}) [1], together with the deliberate avoidance of the dilution and buffering of the test solutions by blood, generated reproducible data which, however, bear little (if any) relevance to clinical practice.

Klement and Arndt misquoted the work of Hynynen and colleagues [3] both in the introduction, associating thiopentone with painful injections (Hynynen's group showed no evidence of pain after thiopentone), and in the discussion in connection with reduced evidence of pain after new formulations of diazepam and etomidate, although neither of these drugs was

studied by Hynynen and colleagues. Using their elegant experimental method of the isolated vein segment, Klement and Arndt could have studied the pain-inducing potential of various i.v. anaesthetic agents without the risk of these reaching the general circulation, thereby generating more useful and relevant information for the daily practice of anaesthesia.

K. S. KHUENL-BRADY
U. WAIBEL
Innsbruck

REFERENCES

1. Klement W, Arndt JO. Pain on i.v. injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. *British Journal of Anaesthesia* 1991; 66: 189-195.
2. Wretling A. Metabolism of fat emulsions for intravenous nutrition. In: Wilkinson AW, Cuthbertson D, eds. *Metabolism and Response to Injury*. London: Pitman, 1976; 69-93.
3. Hynynen M, Korttila K, Tammisto T. Pain on iv injection of propofol (ICI 35 868) in emulsion formulation. *Acta Anaesthesiologica Scandinavica* 1985; 29: 651-652.
4. Sung YF, Weinstein MS, Biddle MR. Comparison of Diprivan (propofol) and thiopental as intravenous induction agents: cardiovascular effects, respiratory change, recovery, and postoperative venous sequelae. *Seminars in Anaesthesia* 1988; 7: 52-56.
5. McCulloch MJ, Lees NW. Assessment and modification of pain on induction with propofol. *Anaesthesia* 1985; 40: 1117-1120.
6. Scott RPF, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; 43: 492-495.
7. Bretschneider H. Osmolalities of commercially supplied drugs often used in anesthesia. *Anesthesia and Analgesia* 1987; 66: 361-362.

Sir,—It is pleasing that our publication has provoked some discussion, particularly as we can cope easily with any criticism:

Our title would be misleading only if one were to ignore the pronoun "some", which we chose deliberately to account for other alternatives. In fact, we were already aware of the exceptional properties of propofol and have demonstrated its analgesic action recently [1].

That most of the drugs mentioned in the paper of Bretschneider [2] have osmolalities less than 1 osmol kg⁻¹ is a spurious argument against osmolality as "principal pain stimulus" because most of these drugs do not evoke pain. In fact, some formulations of those which do evoke pain have osmolalities greater than 6 osmol kg⁻¹—the greatest used in our injection experiments. It is mainly a matter of opinion, if our observations have "little (if any) relevance to clinical practice". In essence, we studied the basic pain-evoking stimuli of injectates, not of drugs. With regard to the clinical implications of our results, we refer to the last paragraph of our discussion.

The reproach of having misquoted Hynynen and colleagues [3] is partially justified. The quotation in the introduction refers to barbiturates in general and to methohexitone in particular but, regrettably, we omitted to add Kewar and Dundee (ref. [4] in our paper) with regard to pain on injections of thiopentone. Admittedly, we misquoted Hynynen and colleagues in the discussion.

We are flattered by the phrase "elegant experimental method of the isolated vein segment", and we agree that we could have studied the pain-inducing potential of clinically used i.v. anaesthetic agents. However, with the exception of propofol [1], the properties of the pharmaceutical formulations appeared to be more relevant as pain-evoking stimuli than the agents themselves. From a theoretical point of view, we tested and proved the hypothesis that unphysiological osmolality and pH *per se* may be responsible for pain on injection. Does it not still hold that "theory is the most practical thing conceivable" [4], stated also with regard to medical sciences just 100 years ago?

W. KLEMENT
J. O. ARNDT
Dusseldorf

REFERENCES

1. Klement W, Arndt JO. Pain on injection of propofol: effects of concentration and diluent. *British Journal of Anaesthesia* 1991; 67: 281-284.
2. Bretschneider H. Osmolalities of commercially supplied drugs often used in anesthesia. *Anesthesia and Analgesia* 1988; 66: 361-362.
3. Hynynen M, Korttila K, Tammisto T. Pain on i.v. injection of propofol (ICI 35868) in emulsion formulation. *Acta Anaesthesiologica Scandinavica* 1985; 29: 651-652.
4. Boltzmann L. On the significance of theories. In: McGuinness B, ed. *Ludwig Boltzmann. Theoretical Physics and Philosophical Problems*. Boston: Dordrecht, 1974.

BOOK REVIEWS

Trauma Anesthesia. Edited by J. K. Sterne and C. Grande. Published by Williams & Wilkins, Baltimore. Pp. 510; indexed; illustrated. Price £54.00.

Trauma Anesthesia reflects the philosophies, experiences and practices of the John Hopkins University School of Medicine and the Maryland Institute for Emergency Medical Services. The book is edited by John Sterne and Christopher Grande (the latter is a significant contributor), both of whom have impeccable backgrounds from which to undertake this daunting task.

The royalties and honoraria from participation in this book are to be donated to the International Trauma Anesthesia and Critical Care Society. This gesture in itself reveals the dedication and commitment of all concerned. How far has the state of the art developed since the publication of *Care of the Trauma Patient* from Dallas, edited by Tom Shires, *Critical Care for Surgical Patients* from Chicago, edited by John Beal and *Textbook of Accident and Emergency Medicine* from Belfast edited by William Rutherford—all classics in their time.

A gentle and thought-provoking Foreword is provided by Peter Safar, whose many honours include Distinguished Service Professor of Resuscitation. This is, indeed, a fitting tribute to a man whose commitment to critical care, resuscitation and trauma has been legendary for more than 50 years. Safar indicates that the contribution of the anaesthetists in the primary management of trauma patients from the time of injury through the perioperative phase until discharge from the critical care facility has been recognized finally by the designation of Trauma Centres in the U.S.A. Moreover, he believes that the anaesthetist, because of his unique expertise, has a duty and obligation to be the instigator of life support. The Preface by the editors develops the concept of trauma anaesthesia as a sub-specialty of anaesthesia. The need for Board Certification and a Trauma Anesthesia Society is explored. Somewhat more contentious is the view that every anaesthetist who cares for trauma patients must have Advanced Trauma Life Support certification (A.T.L.S.). One wonders how the legal profession will react to this proposal. These themes are emphasized and refined continually throughout the book. They are of great importance in the U.K. as we try to develop a sharper focus in responses to the multi-factorial nature of trauma. *Trauma Anesthesia* sets out to enhance the role of the anaesthetist in a major way and describes how we can improve trauma care by understanding the pathophysiology of injury and by sharing the lessons learned from a large trauma facility in Maryland.

There are 18 chapters devoted to trauma, all of which are relevant, well-written and informative. Each chapter commences with a list of contents for ease of reference and ends with a summary. The quality of the latter is not consistently good. Tables, illustrations and photographs are of a high standard.

Space does now allow me to comment on individual chapters, except to say that the chapter on "The Pregnant Patient" is rather unique and reveals that 2.5% of trauma

patients admitted to MIEMSS are pregnant. A chapter on "Occupational Hazards for Trauma Health Care Workers" is novel, but relevant. Apparently, between 13 and 16% of patients are HIV+, but hepatitis B poses a greater risk, and Rice and Cullen recommend that all health care workers should be vaccinated. The current interest in Clinical Information Systems is not neglected and the advice presented on Legal and Ethical Issues is also timely and welcome.

The "bread and butter" topics, such as airway management, shock resuscitation, CNS trauma, blood component therapy and injuries to craniocervicofacial complex are discussed comprehensively. I was pleased to see a separate chapter for paediatric patients, who are often neglected in trauma literature. A chapter on transport of the trauma patient, which follows conventional lines for patients outside hospital, highlights a similar need for high quality transport to be available within the hospital.

I can recommend this book unreservedly to all involved in trauma care, even though it is directed principally at anaesthetists. Trauma anaesthesia has come a long way in the past 10 years. The book is good value at £54.00.

D. L. Coppel

Emergency Drug Therapy, 1st Edn. Edited by W. G. Barsan, M. S. Jastremski and S. A. Syverud. Published by W. B. Saunders & Co., Philadelphia. Pp. 655; indexed; illustrated. Price £44.00.

The title of this book is possibly misleading, in that it might suggest another manual designed for the white coat pocket, but this is far from the case. *Emergency Drug Therapy* represents a long-awaited textbook on the pharmacological management of the critically ill patient. It contains 26 chapters from 30 contributors who, in the main, work within the field of emergency and critical care medicine. By legitimately including crystalloids and colloids as drugs, the editors have been able to cover management of most conditions presenting in the critical care environment.

The opening four chapters discuss pharmacokinetics and the changes that occur in the pregnant and the paediatric patient. The remaining chapters deal with specific drug groups—for example, antiarrhythmics and vasoactive drugs. Despite the many contributors, the book maintains consistency by applying the same format to each condition for which the drugs are indicated: diagnosis, indications for treatment, drug treatment outline and discussion.

Inevitably, the transatlantic origins of the book lead to some interesting omissions and different emphasis; for example, amiodarone is not available and therefore not included in the chapter on antiarrhythmics nor enoximone under vasoactive drugs; fluid management of hypovolaemia is based on crystalloid resuscitation as the first line treatment. Nevertheless, the majority of clinicians will find the treatments advocated to be rational and well presented.

This book will provide a valuable source of reference for all examination candidates, particularly at Parts 1 and 3 of the F.C.Anaes. examinations, and will be a welcome addition to the library of the intensivist.

G. W. Jones

Handbook of Obstetric Anaesthesia. By A. S. Buchan and G. H. Sharwood-Smith. Published by W. B. Saunders, London. Pp. 115; indexed; illustrated. Price £9.95.

This book is designed to reside in the pocket of the on-call trainee obstetric anaesthetist. It should replace neither study of standard obstetric anaesthetic textbooks nor adequate consultant supervision and availability.

Most obstetric units will (or should) have their own obstetric anaesthetic booklet regularly updated. The inclusion of many

clear diagrams, flow charts for management, concise tables and a selection of up-to-date references suggests that this book is more than an in-house manual. However, background obstetric anaesthetic knowledge is required to interpret intelligently some of the advice—for example management of total spinal anaesthesia, or failed intubation drill—and apply it to a particular patient. Therefore the book will be of limited interest to midwives and, perhaps, obstetricians.

Some of our trainees felt that advice on "How to manage the patchy epidural" "How to extend an epidural quickly for operative delivery" was an important omission.

Perhaps this book should be quickly read together with the in-house booklet, then returned to the shelf while the more major textbooks are studied. I suspect that the trainee at 04:00 will consult the "large tomes" if these are readily available. If not, this book will serve its purpose and, costing only £9.95, probably should have a place in every unit.

R. Macdonald

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

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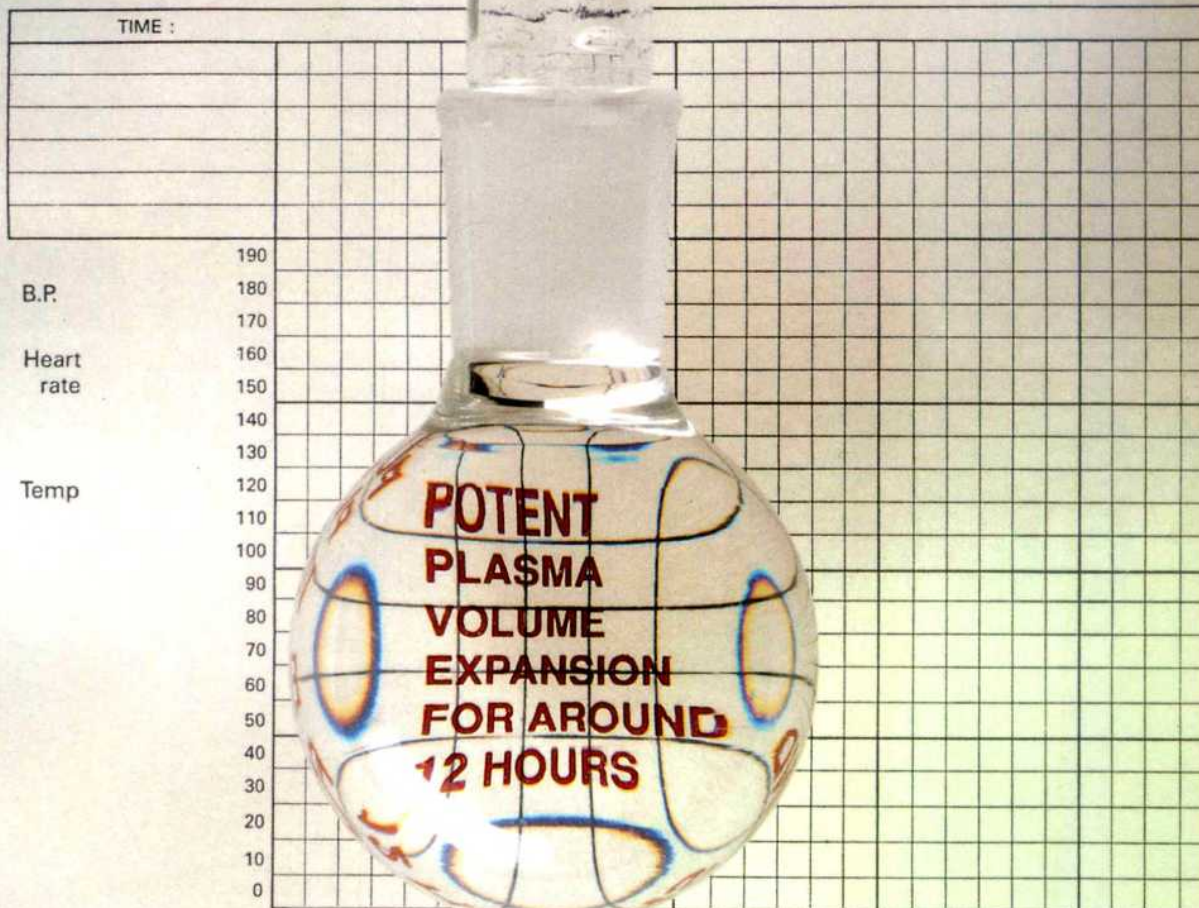
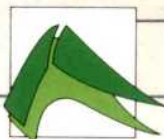
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CONTENTS

	PAGE		PAGE
EDITORIALS:		Interaction between betamethasone and vecuronium <i>S. M. Parr, B. J. Robinson, D. Rees and D. C. Galletly</i>	447
I. Silent myocardial ischaemia in preoperative patients: what does it mean and what should be done about it?.....	367	REVIEW ARTICLE	
<i>D. P. de Bono and E. L. Rose</i>		The prone position for the surgical patient: a historical review of the principles and hazards ...	452
II. Drug biotransformation by the kidney: how important is it, and how much do we really know?	369	<i>J. M. Anderton</i>	
<i>J. W. Sear</i>		RAPID COMMUNICATIONS	
ORIGINAL ARTICLES		Effectiveness of preoxygenation in morbidly obese patients	464
Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population ...	373	<i>M. C. Berthoud, J. E. Peacock and C. S. Reilly</i>	
<i>A. D. Muir, M. K. Reeder, P. Foëx, O. J. M. Ormerod, J. W. Sear and C. Johnston</i>		Metabolic response to colonic surgery: extradural vs continuous spinal.....	467
Physiological disposition of i.v. morphine in sheep ..	378	<i>J. Webster, M. Barnard and F. Carli</i>	
<i>P. A. Sloan, L. E. Mather, C. F. McLean, A. J. Rutten, R. L. Nation, R. W. Milne, W. B. Runciman and A. A. Somogyi</i>		Rapid inhalation induction with isoflurane in humidified carrier gas	470
Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia	387	<i>P. V. van Heerden, D. F. Morrell and P. Becker</i>	
<i>Y. Natto, S. Tamai, K. Shingu, R. Fujimori and K. Mori</i>		CASE REPORTS	
Midazolam modifies pancreatic and anterior pituitary hormone secretion during upper abdominal surgery	390	Unsuspected extradural catheterization in an interscalene block	473
<i>J. P. Desborough, G. M. Hall, G. R. Hart and J. M. Burrin</i>		<i>L. B. Cook</i>	
Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia	397	Superior sagittal sinus thrombosis after internal jugular vein cannulation	476
<i>L. Delaunay, F. Bonnet and P. Duvaldestin</i>		<i>P. H. Stephens, G. Lemox, N. Hirsch and D. Miller</i>	
A comparison of dexmedetomidine, an α_2 -adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery ..	402	Delayed pneumothorax after subclavian vein catheterization and positive pressure ventilation ..	480
<i>R. Aantaa, M.-L. Jaakola, A. Kallio, J. Kanto, M. Scheinin and J. Vuorinen</i>		<i>M. C. Cronen, P. W. Cronen, P. Arino and K. Ellis</i>	
Effects of adenosine triphosphate on the cardiovascular response to tracheal intubation	410	Repair of traumatic transection of the thoracic aorta: esmolol for intraoperative control of arterial pressure	483
<i>K. Mikawa, N. Maekawa, H. Kaetsu, R. Goto, H. Yaku and H. Obara</i>		<i>S. G. Fenner, A. Mahoney and J. N. Cashman</i>	
Effects of pindolol on the cardiovascular response to tracheal intubation	416	APPARATUS	
<i>K. Mikawa, N. Maekawa, R. Goto, H. Kaetsu, M. Hasegawa, M. Yaku and H. Obara</i>		The pneuPAC hyperbaric variant HB: a ventilator suitable for use within a one-man hyperbaric chamber	488
Effect of cisapride on morphine absorption after oral administration of sustained-release morphine	421	<i>M. J. Pittall, S. J. Hunter and L. Jones</i>	
<i>D. J. Rowbotham, K. Milligan and P. McHugh</i>		Fresh gas utilization of eight circle systems	492
Gastric emptying and small bowel transit in male volunteers after i.m. ketorolac and morphine	426	<i>A. M. Zbinden, P. Feigenwinter and M. Hutmacher</i>	
<i>M. K. Yee, W. D. Evans, P. E. Facey, M. W. J. Hayward and M. Rosen</i>		CORRESPONDENCE	
Preliminary study to assay plasma amethocaine concentrations after topical application of a new local anaesthetic cream containing amethocaine ..	432	Inhalation induction of anaesthesia with isoflurane in children	500
<i>B. Mazumdar, A. A. Tomlinson and G. C. Faulder</i>		Unexpected, difficult laryngoscopy	501
Systemic fentanyl enhances the spread of spinal analgesia produced by lignocaine	437	Desaturation during total knee replacement	502
<i>A. Fassoulaki, C. Sarantopoulos and S. Chondrelli</i>		Atracurium and suxamethonium	502
Effect of Pa_{O_2} on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat	440	Training in fibreoptic laryngoscopy	503
<i>W. L. Young, A. I. Barkai, I. Prohovnik, H. Nelson and M. Durkin</i>		Reporting of deaths	503
		Antagonism of benzodiazepine sedation with flumazenil	504
		Predicting difficult intubation	505
		Diprivan intensive care sedation in children	505
		Systolic arterial pressure as a monitor of depth of anaesthesia	506
		Pain on i.v. injection	506
		BOOK REVIEWS	
		<i>Trauma Anaesthesia</i>	508
		<i>Emergency Drug Therapy</i>	508
		<i>Handbook of Obstetric Anaesthesia</i>	509

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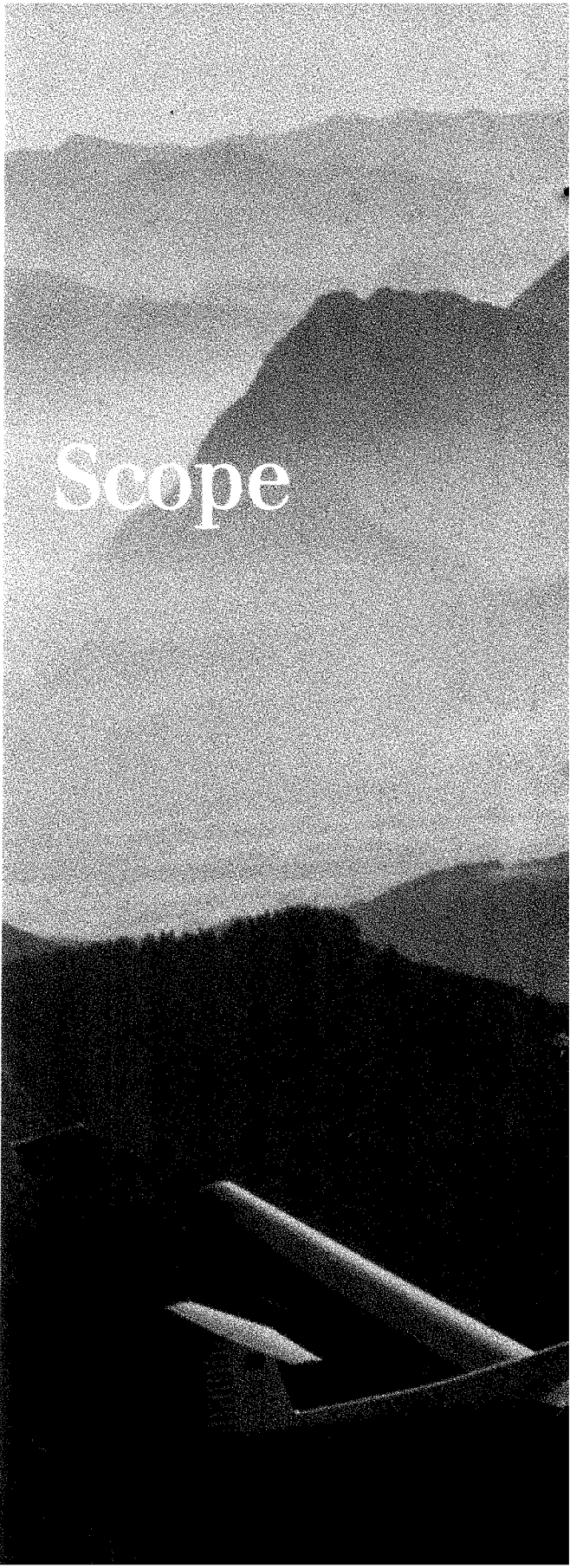
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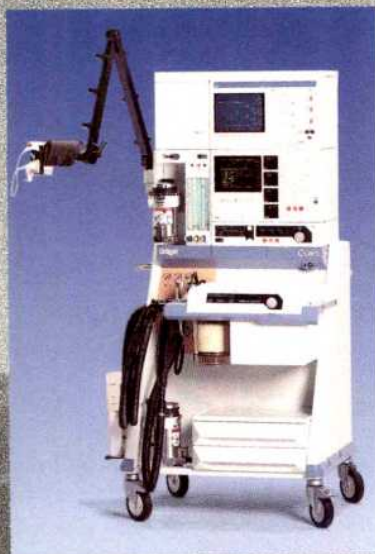
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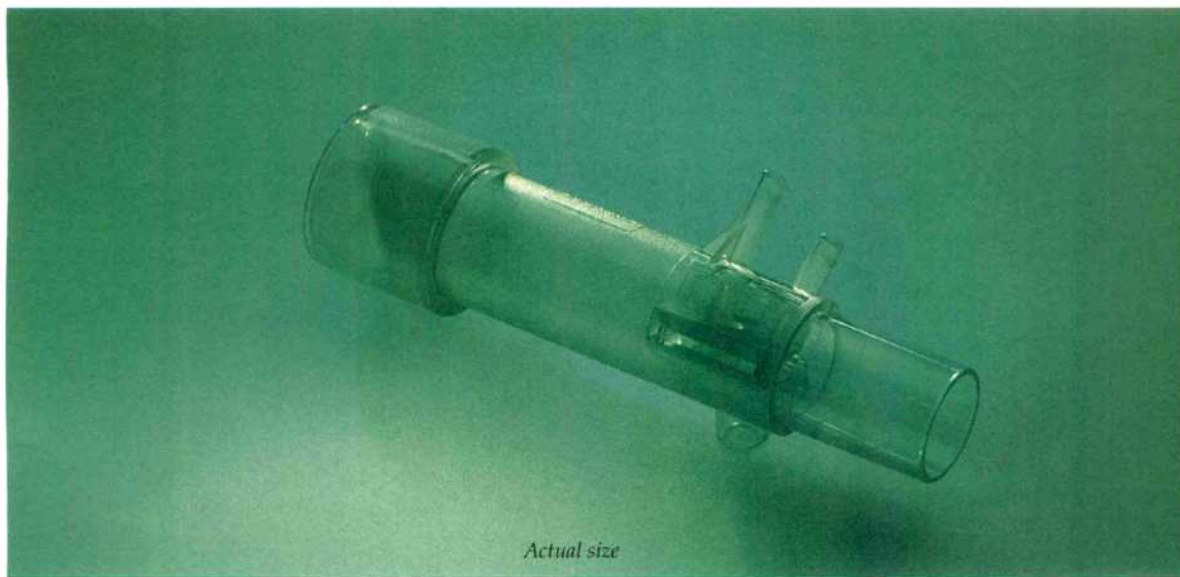
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Überweisung
D.-J. Gaida, H.W. Gervais, D. Maurer,
K.-H. Leyrer, B. Eberle
Anästhesiologische Probleme beim
Tajikistan-Syndrom
[Management of anaesthesia in
Tajikistan syndrome] 1

P. Sauc, D. Kettler, H. Sonntag
Hämodynamische Parameter zur Abschätzung
des myokardialen Sauerstoffverbrauchs in der
Anästhesie
(Hemodynamic variables reflecting myocardial
oxygen consumption in anaesthesia) 7

C. Spies, U. Ziemann
E. Martin
Vergleich von Enturen und Propolol bei
thrombozytopenischen Eingriffen
(Comparison of enturen and propolol
in surgery) 14

H. Wurf, W. Jechtrup
Intraoperative Katheteranästhesie bei
mit Rippenverletzungen
(Intraoperative analgesia with epidural
catheters in patients with multiple rib fractures)

M. Tryba, J. Linde, G. Voshage, M.
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Zentrum Anästhesiologie der Universität Göttingen

Hemodynamic variables reflecting myocardial oxygen consumption in anesthesia

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product that exclude myocardial ischemia. Because of regional differences in the myocardial oxygen consumption, ischemia cannot be detected solely from arteriovenous lactate differences. It is not advisable to assume "safe limits" of hemodynamic variables. Rather, individual monitoring is mandatory during anesthesia and operation. Adequate close monitoring of blood pressure, heart rate and ECG may help to disclose myocardial ischemia.

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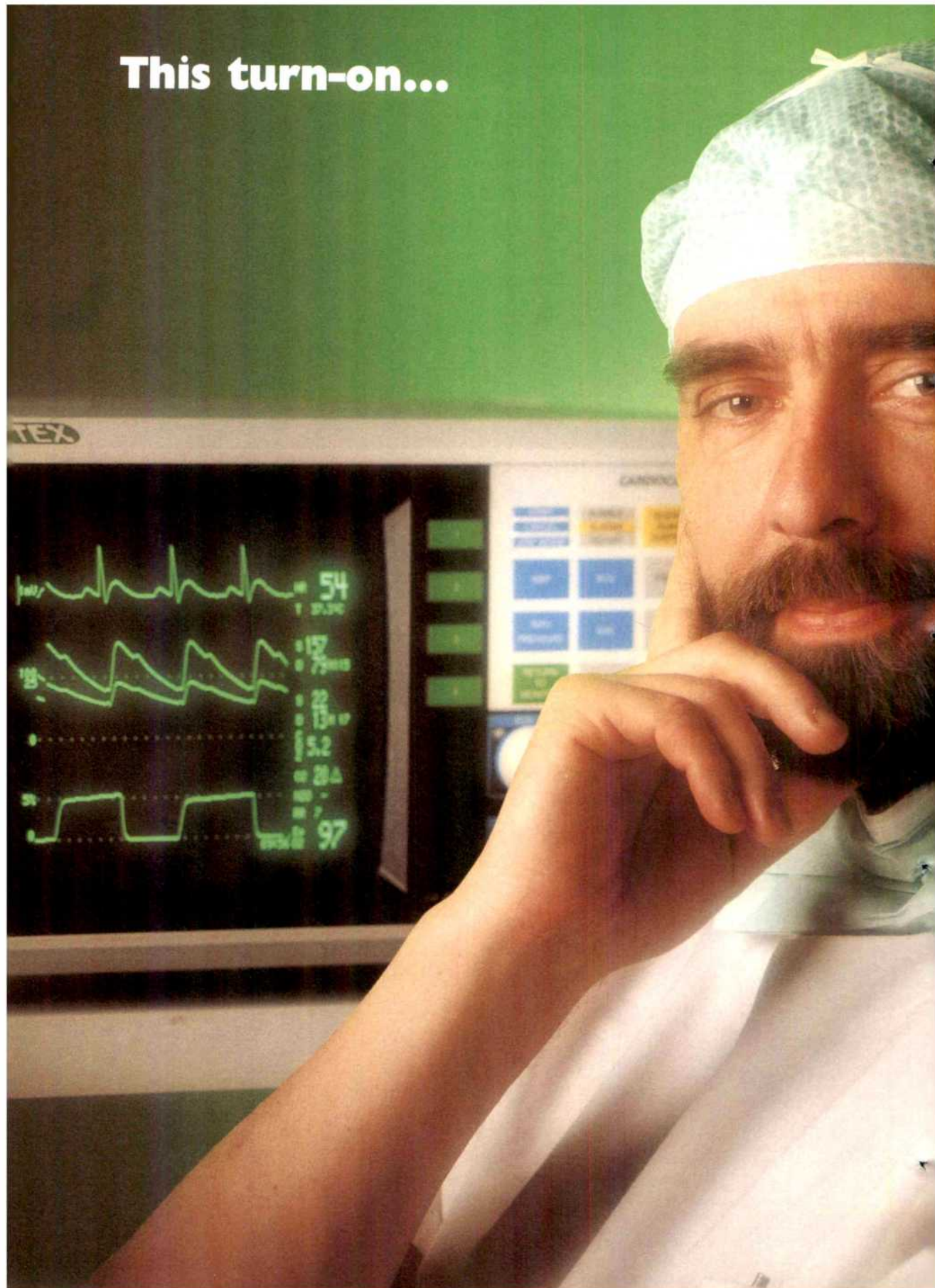


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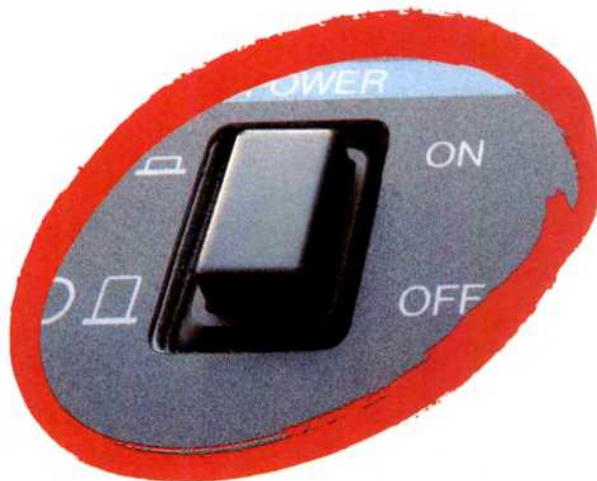
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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 67, No. 5

NOVEMBER 1991

EDITORIAL I

RESISTANCE TO NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

Most anaesthetists have had the clinical experience of being unable to produce adequate neuromuscular block for surgical access despite repeated, and what occasionally might be considered excessive, doses of a non-depolarizing neuromuscular blocking agent. The cause of this resistance usually remains unexplained at the end of surgery and cannot be clarified by routine plasma screening. Sometimes apparent resistance results from no factor more complicated than simple error: failure to store the drug at the recommended temperature, errors in dilution, or even use of the wrong substance. When these simple possibilities have been excluded, altered plasma protein binding or volume of distribution should be considered. The effect of an increased number of postsynaptic acetylcholine receptors may also be relevant, as may the patient's temperature and metabolic state or the isomeric mixture of the drug in the vial.

Plasma protein binding

Most drugs bind to at least one of three plasma proteins: *albumin* (which has three separate binding sites), *alpha₁ acid glycoprotein* (AAG) (one of the *alpha₁* globulins) or *lipoproteins* [1]. Drugs may bind to more than one site on the albumin molecule and to more than one plasma protein. In general, acidic drugs are believed to bind to albumin and basic drugs to AAG [2]. It would be expected that non-depolarizing neuromuscular blocking agents, with their basic quaternary amine structure, would bind predominantly to AAG, but Stovner, Theodorsen and Bjelke suggested in 1971 that alcuronium [3] and gallamine [4] are bound predominantly to plasma albumin, in contrast with pancuronium [4], for which no specific binding pattern could be detected. Baraka and Gabali [5] found a highly significant correlation between the serum concentration of gamma globulin and tubocurarine requirement, with a weaker relationship to the albumin con-

centration. It seems, therefore, that even the basic principles of binding of drugs to plasma proteins cannot be applied simply to non-depolarizing neuromuscular blocking agents. Measuring plasma protein binding is fraught with problems, however [1], and the validity of many of the earlier reports is questionable. For example, it may have been difficult to differentiate between *alpha₁* and gamma globulin in earlier studies, and this would explain the discrepancy with tubocurarine. More research is clearly needed on plasma protein binding of neuromuscular blocking agents.

It is important to remember that the total plasma protein binding of neuromuscular blocking drugs compared with such drugs as diazepam (98%) and alfentanil (92%) [1] is not great (table I). In practice, changes in the degree of plasma protein binding are of clinical importance only if protein binding is greater than 85%, when only a small decrease in the amount of bound drug increases to a highly significant degree the free fraction of the drug, which is responsible for the clinical effect [1, 2]. Because non-depolarizing drugs are not highly bound, any slight change in the degree of protein binding of a neuromuscular blocking agent is unlikely to be of clinical significance.

Clinical resistance is seen most often in chronic disease, but no change in the plasma protein binding of pancuronium [8] or tubocurarine [9]

TABLE I. *Plasma protein binding of the non-depolarizing neuromuscular blocking agents* [1, 6, 7]. * By an indirect in vitro method [7]; † [unpublished data: J. M. Hunter and T. N. Calvey]

	Percent bound
Alcuronium	40
Atracurium	282*
	37†
Pancuronium	11-29
Tubocurarine	43-51
Vecuronium	30

TABLE II. *Volume of distribution of non-depolarizing neuromuscular blocking agents in health and disease (mean values); *P < 0.05 compared with healthy group*

	Volume of distribution (ml kg ⁻¹)					
	Renal effects			Hepatic effects		
	Healthy	Chronic renal failure	Ref.	Healthy	Cirrhotic liver disease	Ref.
Atracurium	182	224	[16]	202	282*	[17]
Pancuronium	262	296	[18]	279	416*	[19]
Vecuronium	194	239	[20]	246	253	[21]

has been found in renal disease, or of tubocurarine [9], pancuronium or vecuronium [6] in cirrhotic liver disease, although plasma protein concentrations are known to alter in these circumstances. However, altered binding of basic drugs to AAG in acute disease states may explain the resistance to atracurium reported in this issue by Tatman, Wrigley and Jones [10]. Plasma concentrations of AAG, an acute phase protein, are increased in several acute conditions, including burns, myocardial infarction, severe infection, malignancy, Crohn's disease, ulcerative colitis and renal transplantation [1]. They are increased also in some types of chronic renal failure [2]. This increased binding to an acute phase protein, with a subsequent reduction in the free, active fraction of the drug may explain, therefore, the occasional unexpected difficulty in obtaining adequate neuromuscular block, especially during emergency surgery; but whether it is responsible for the hyposensitivity to tubocurarine demonstrated after thermal injury has been questioned [11].

Altered volume of distribution

Since the first report by Dundee and Gray [12], it has been demonstrated that patients with cirrhotic liver disease, of various aetiologies, are resistant to small bolus doses, not only of tubocurarine but also of pancuronium [13], atracurium and vecuronium [14]. There is some evidence of a similar resistance in chronic renal failure [15]. This phenomenon may be caused, not by an increase in the protein binding of the neuromuscular blocking agent which would *decrease* the volume of distribution of the drug, but by an *increased* volume of distribution of these water soluble, highly ionized drugs in conditions in which there is a significant increase in extracellular fluid, with or without frank oedema. The

increased volume of distribution of a bolus dose of a neuromuscular blocking agent is associated with a smaller plasma concentration and hence a reduced effect. Repeated increments of the blocking drug eventually increase the plasma concentration sufficiently to produce satisfactory clinical conditions, but difficulty in eventual antagonism of residual neuromuscular block may ensue because of delayed clearance of the relaxant caused by the disease state. The volumes of distribution of some non-depolarizing neuromuscular blocking agents in health and disease are shown in table II.

Increased number of receptor sites

Where resistance to non-depolarizing neuromuscular blocking agents has been reported in chronic disease states involving voluntary muscle, a pharmacodynamic rather than a pharmacokinetic problem is envisaged. The affected muscles in hemiplegia, for example, are thought to be resistant because of increase in postsynaptic acetylcholine receptors [22], as is possibly the case in multiple sclerosis [23] and disuse atrophy [24]. In these chronic conditions, however, the anaesthetist is usually aware of the pre-existing pathology and should not, therefore, experience *unexpected* resistance to a non-depolarizing neuromuscular blocking drug. In many muscle disorders, such as myasthenia gravis and myotonia dystrophica, increased sensitivity to non-depolarizing blockers is common but, because both *upgrading* and *downgrading* of postsynaptic acetylcholine receptors can occur in these conditions, resistance may occasionally be encountered.

Treatment with the antiepileptic drug phenytoin, has been associated with resistance to all the non-depolarizing neuromuscular blockers, except atracurium. It has been postulated that this may

be caused by an increase in the number of postsynaptic receptors, a decrease in their sensitivity or even a presynaptic effect [25].

Body temperature and pH

It is interesting to speculate on the relationship between an increase in body temperature and the degree of block obtained by the non-depolarizing neuromuscular blocking agents. From animal work it has been suggested that an increase in temperature may reduce the duration of action of atracurium, as Hofmann elimination is potentiated [26], but in such circumstances it may be that increased binding of not only atracurium but all these drugs to acute phase proteins is a factor in the decreased duration of action occasionally encountered in pyrexial patients.

A respiratory alkalosis has been shown to antagonize the neuromuscular block produced by tubocurarine [27], pancuronium and vecuronium [28], although the effect of metabolic alkalosis is more controversial; indeed, it has been suggested that the latter may potentiate the block. Hyperkalaemia may also be expected to decrease the duration of drug-induced neuromuscular block, as it lowers the resting membrane potential of the muscle membrane, thus promoting depolarization and muscle contraction.

Isomeric mixtures

A vial of any optically active drug may contain more than one isomer; each isomer may have a different elimination half-life and rate of clearance from the body. A vial of atracurium may contain up to 10 isomers. The three geometrical isomer groups present are the cis-cis, cis-trans and trans-trans groups. The cis-cis group (58%), which produces the required clinical effect, has a half-life of about 23 min. The cis-trans group (36%) has a biexponential half-life with a rapid phase of 2.3 min and the trans-trans group (6%) has such a short half-life that, in the small concentrations found in the plasma after a bolus injection, it is difficult to measure [29]. If the last two of these isomers are present in greater than expected concentrations in a vial, more rapid than expected recovery may occur. This is, however, an unlikely cause of unexpected resistance to atracurium and the resistance is only apparent, not real.

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REFERENCES

1. Wood M. Plasma drug binding: implications for anesthesiologists. *Anesthesia and Analgesia* 1986; **65**: 786-804.
2. Routledge PA. The plasma protein binding of basic drugs. *British Journal of Clinical Pharmacology* 1986; **22**: 499-506.
3. Stovner J, Theodorsen L, Bjelke E. Sensitivity to tubocurarine and alcuronium with special reference to plasma protein pattern. *British Journal of Anaesthesia* 1971; **43**: 385-391.
4. Stovner J, Theodorsen L, Bjelke E. Sensitivity to gallamine and pancuronium with special reference to serum proteins. *British Journal of Anaesthesia* 1971; **43**: 953-958.
5. Baraka A, Gabali F. Correlation between tubocurarine requirements and plasma protein pattern. *British Journal of Anaesthesia* 1968; **40**: 89-93.
6. Duvaldestin P, Henzel D. Binding of tubocurarine, fazadinium, pancuronium and Org NC45 to serum proteins in normal man and in patients with cirrhosis. *British Journal of Anaesthesia* 1982; **54**: 513-516.
7. Foldes FF, Deery A. Protein binding of atracurium and other short-acting neuromuscular blocking agents and their interaction with human cholinesterases. *British Journal of Anaesthesia* 1983; **55**: 31S-34S.
8. Wood M, Stone WJ, Wood AJJ. Plasma binding of pancuronium: effects of age, sex and disease. *Anesthesia and Analgesia* 1983; **62**: 29-32.
9. Ghonheim MM, Kramer E, Bannow R, Pandya H, Routh JI. Binding of d-tubocurarine to plasma proteins in normal man and in patients with hepatic or renal disease. *Anesthesiology* 1973; **39**: 410-415.
10. Tatman AJ, Wrigley SR, Jones RM. Resistance to atracurium in a patient with an increase in plasma alpha₁ globulins. *British Journal of Anaesthesia* 1991; **67**: 623-625.
11. Leibel WS, Martyn JAJ, Szyfelbein SK, Miller KW. Elevated plasma binding cannot account for the burn-related d-tubocurarine hyposensitivity. *Anesthesiology* 1981; **54**: 378-382.
12. Dundee JW, Gray TC. Resistance to d-tubocurarine chloride in the presence of liver damage. *Lancet* 1953; **2**: 16-17.
13. Nana A, Cardan E, Leitersdorfer T. Pancuronium bromide. Its use in asthmatics and patients with liver disease. *Anaesthesia* 1972; **27**: 154-158.
14. Bell CF, Hunter JM, Jones RS, Utting JE. Use of atracurium and vecuronium in patients with oesophageal varices. *British Journal of Anaesthesia* 1985; **57**: 160-168.
15. Hunter JM, Jones RS, Utting JE. Comparison of vecuronium, atracurium and tubocurarine in normal patients and patients with no renal function. *British Journal of Anaesthesia* 1984; **56**: 941-951.
16. Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis PJ. The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. *Anesthesiology* 1984; **61**: 699-702.
17. Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. *British Journal of Anaesthesia* 1989; **62**: 177-183.
18. Somogyi AA, Shanks CA, Triggs EJ. The effect of renal failure on the disposition and neuromuscular blocking

- action of pancuronium bromide. *European Journal of Clinical Pharmacology* 1977; 12: 23-29.
19. Duvaldestin P, Agoston S, Henzel D, Kersten UW, Desmonts JM. Pancuronium pharmacokinetics in patients with liver cirrhosis. *British Journal of Anaesthesia* 1978; 50: 1131-1135.
 20. Fahey MR, Morris RB, Miller RD, Nguyen T-L, Upton RA. Pharmacokinetics of Org NC45 (Norcuron) in patients with and without renal failure. *British Journal of Anaesthesia* 1981; 53: 1049-1053.
 21. Lebrault C, Berger JL, D'Hollander AA, Gorneli R, Henzel D, Duvaldestin P. Pharmacokinetics and pharmacodynamics of vecuronium (Org NC45) in patients with cirrhosis. *Anesthesiology* 1985; 62: 601-605.
 22. Graham DH. Monitoring neuromuscular block may be unreliable in patients with upper-motor-neuron lesions. *Anesthesiology* 1980; 52: 74-75.
 23. Brett RS, Schmidt JH, Gage JS, Schartel SA, Poppers PJ. Measurement of acetylcholine receptor concentration in skeletal muscle from a patient with multiple sclerosis and resistance to atracurium. *Anesthesiology* 1987; 66: 837-839.
 24. Gronert GA. Disuse atrophy with resistance to pancuronium. *Anesthesiology* 1981; 55: 547-549.
 25. Ornstein E, Matteo RS, Schwartz AE, Silverberg PA, Young WL, Diaz J. The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. *Anesthesiology* 1987; 67: 191-196.
 26. Neill EAM, Chapple DJ, Thompson CW. Metabolism and kinetics of atracurium: an overview. *British Journal of Anaesthesia* 1983; 55: 23S-25S.
 27. Katz RL, Wolf CE. Neuromuscular and electromyographic studies in man: effect of hyperventilation, carbon dioxide inhalation and d-tubocurarine. *Anesthesiology* 1964; 25: 781-787.
 28. Gencarelli PJ, Swen J, Koot HWJ, Miller RD. The effects of hypercarbia and hypocarbia on pancuronium and vecuronium neuromuscular blockades in anesthetised humans. *Anesthesiology* 1983; 59: 376-380.
 29. Tsui D, Graham GG, Torda TA. The pharmacokinetics of atracurium isomers *in vitro* in humans. *Anesthesiology* 1987; 67: 722-728.

EDITORIAL II

JAW STIFFNESS—AN ILL UNDERSTOOD CONDITION

Many terms have evolved to describe jaw tightness which occurs within anaesthesia. Such terms include "masseter spasm" [1], "masseter myotonia" [2], "suxamethonium spasm" [3], "masseter muscle rigidity" [4] and "masseteric muscle spasm" [5]. Unfortunately, these terms often convey the impression of a scientific precision which does not exist. Whichever term is used refers merely to a rather non-specific increase in the tone of the jaw muscles which may occur during several clinical situations.

It is generally believed that this rather nebulous condition, which occurs after the administration of suxamethonium, is more frequent in children than adults, occurs usually at induction of anaesthesia and on occasions may lead to difficulty with tracheal intubation. As the majority of such reports have originated from retrospective surveys (in some instances merely from the perusal of anaesthetic records), there is a clear need for correctly controlled prospective studies of this phenomenon. In addition, the condition may be misdiagnosed: if inadequate doses of suxamethonium are administered or insufficient time allowed for the drug to act, the jaw muscles may be incompletely relaxed when tracheal intubation is attempted and anaesthetists mistakenly may make a diagnosis of "masseter spasm". Furthermore, jaw tightness after administration of suxamethonium is a subjective diagnosis, and anaesthetists may differ considerably in their threshold of attaching a label in equivocal cases.

For these reasons, reported instances of jaw tightness are very variable. An often-quoted study from the United States suggested an incidence in children of 1:800 and identified a subgroup of patients who received both halothane and suxamethonium in which the incidence was reported to be 1:100 [6]. In another survey, a group of paediatric patients undergoing strabismus surgery who received these agents, had an astonishingly high incidence of 1:36 [7]. In contrast, in Europe, jaw tightness appears to be a less common phenomenon. In Denmark, the incidence in adults and children has been described as 1:12000 [8],

and in the U.K. the incidence in children has been estimated at about 1:100000 [5].

It has been demonstrated recently that an increase in masseter stiffness may accompany the administration of suxamethonium. Several ingenious methods have been used to attempt to measure this effect [9–11]. It has been shown that the increase in jaw stiffness is related to the dose of suxamethonium administered [10] and is not attenuated by prior administration of small doses of non-depolarizing neuromuscular blocking agents [12]; however, full paralysing doses of non-depolarizing agents prevent this response [12]. The increase in stiffness may occur in other muscle groups, but is noticeable especially in the masseter because it is a powerful muscle with an action relatively unopposed by the weaker jaw-opening muscles. Also, as an upper airway muscle, its action is assessed easily by the anaesthetist.

This suxamethonium-induced increase in jaw stiffness varies in magnitude. Consequently, more severe forms of this condition may have been incorrectly termed "masseter spasm" in the past. The normal response to suxamethonium is an increase in muscle stiffness which is maximal at the time of muscle fasciculations, is transient and is not accompanied by other signs of hypermetabolism. A marked increase in jaw stiffness which cannot be overcome manually and lasts longer than several minutes is frequently termed masseter spasm, but there is dispute as to the diagnostic significance of this in relation to malignant hyperthermia (MH).

Whilst prolonged jaw stiffness may be an early sign of MH [1, 13], it is quite evident that it does not invariably precede or proceed to this serious syndrome. It is one of several clinical signs which may accompany, but are not specific for, MH [14]. The coincidence of jaw tightness and MH is in the order of 50%; reportedly less in adults than children [15]. Earlier studies which suggested a closer correlation have been criticized for using inadequate MH susceptibility tests [16]. Analysis of paediatric data is made more difficult by the fact that children, who allegedly have a greater

incidence of jaw stiffness in response to suxamethonium, are often not subjected to muscle biopsy in cases of suspected MH, and therefore there is greater difficulty in making a diagnosis. It is currently recommended that signs of hypermetabolism (including metabolic and respiratory acidosis, increased core temperature, and increased end-tidal carbon dioxide concentrations), should be awaited after increased jaw stiffness is noted, before a diagnosis of MH is contemplated [17].

Jaw stiffness after administration of suxamethonium therefore bears only a loose association with the presence of MH. In the absence of other definitive signs of hypermetabolism, it would not be justifiable to subject patients to muscle biopsies in order to obtain *in vitro* contracture responses to halothane and caffeine [18]. It is to be hoped that a less invasive method of confirming or refuting MH susceptibility, based on gene localization, may become available [19], and if so, would permit investigation of a larger section of the potential MH susceptible population.

Jaw stiffness following suxamethonium remains a nebulous condition. The use of a variety of terms with more precise physiological significance has served merely to confuse rather than to illuminate this condition and, to date, a majority of information which exists is based upon uncontrolled retrospective data. There is a place for future, carefully controlled prospective investigation of the changes in jaw tone which occur on induction of anaesthesia in adult and paediatric populations.

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REFERENCES

- Donlon JV, Newfield P, Sreter F, Ryan JF. Implications of masseter spasm after succinylcholine. *Anesthesiology* 1978; 49: 298-301.
- Leary NP, Ellis FR. Masseter myotonia with suxamethonium. *British Journal of Anaesthesia* 1988; 60: 345P.
- Ellis FR, Halsall PJ. Suxamethonium spasm. A differential diagnostic conundrum. *British Journal of Anaesthesia* 1984; 56: 381-383.
- Rosenberg H, Fletcher JE. Masseter muscle rigidity and malignant hyperthermia susceptibility. *Anesthesia and Analgesia* 1986; 65: 161-164.
- Christian AS, Ellis FR, Halsall PJ. Is there a relationship between masseteric muscle spasm and malignant hyperthermia? *British Journal of Anaesthesia* 1989; 62: 540-544.
- Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia: incidence and implications. *Anesthesiology* 1984; 61: 772-775.
- Carroll JB. Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. *Anesthesiology* 1987; 67: 559-561.
- Ording H. Incidence of malignant hyperthermia in Denmark. *Anesthesia and Analgesia* 1985; 64: 700-704.
- Van der Spek AF, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. The effects of succinylcholine on mouth opening. *Anesthesiology* 1987; 67: 459-465.
- Plumley MP, Bevan JC, Saddler JM, Donati F, Bevan DR. Dose related effects of succinylcholine on adductor pollicis and masseter muscles in children. *Canadian Journal of Anaesthesia* 1990; 37: 15-20.
- Leary NP, Ellis FR. Masseteric muscle spasm as a normal response to suxamethonium. *British Journal of Anaesthesia* 1990; 64: 488-492.
- Smith CE, Saddler JM, Bevan JC, Donati F, Bevan DR. Pretreatment with non-depolarizing neuromuscular blocking agents and succinylcholine-induced increases in resting jaw tension in children. *British Journal of Anaesthesia* 1990; 64: 577-581.
- Barlow M, Isaacs H. Malignant hyperpyrexia deaths in a family. *British Journal of Anaesthesia* 1970; 42: 1072-1076.
- Hackl W, Mauritz W, Schemper M, Winkler M, Sporn P, Steinbereithner K. Prediction of malignant hyperthermia susceptibility: statistical evaluation of clinical signs. *British Journal of Anaesthesia* 1990; 64: 425-429.
- Allen GC, Rosenberg H. Malignant hyperthermia susceptibility in adult patients with masseter muscle rigidity. *Canadian Journal of Anaesthesia* 1990; 37: 31-35.
- Ellis FR, Halsall PJ. Improper test may account for high incidence of malignant hyperthermia associated with masseter spasm. *Anesthesiology* 1986; 64: 291.
- Van der Spek AF, Reynolds PI, Fang WB, Ashton-Miller JA, Stohler CS, Schork MA. Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular blockers. *British Journal of Anaesthesia* 1990; 64: 21-27.
- European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia. *British Journal of Anaesthesia* 1984; 54: 1267-1269.
- MacLennan DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk RG, Frodis W, Britt BA, Worton RG. Ryanodine receptor is a candidate for predisposition to malignant hyperthermia. *Nature (London)* 1990; 343: 559-561.

AIRWAY OBSTRUCTION ASSOCIATED WITH THE USE OF THE GUEDEL AIRWAY

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SUMMARY

Soft tissue lateral neck radiography was used in 22 male patients older than 60 yr, to determine the cause of pharyngeal airway obstruction during anaesthesia, before and after insertion of a Guedel airway. In six of the patients, the airway was radiologically and clinically clear with the head in the neutral position. Nine patients showed obstruction of the airway by a "shelf" of tongue, but seven were cleared clinically by dorsiflexion at the atlanto-occipital joint, and the remaining two by the Esmarch-Heiberg manoeuvre. In four of the 22 patients, the Guedel airway was lodged in the vallecula in the neutral position. This was cleared clinically by dorsiflexion at the atlanto-occipital joint in all these patients. In three patients the Guedel airway was obstructed by the epiglottis, but this was cleared by dorsiflexion at the atlanto-occipital joint in two; in the third patient, the Guedel airway slipped into the vallecula after dorsiflexion at the atlanto-occipital joint and remained there despite the Esmarch-Heiberg manoeuvre. There was only one instance in 66 trials of a clinically obstructed airway without an apparent radiological cause. However, there were 10 instances in 66 trials of a clinically clear airway with an apparent radiological cause for obstruction.

KEY WORDS

Airway: Guedel, obstruction.

prevent partial or complete obstruction of the airway, for example dorsiflexion at the atlanto-occipital joint or an Esmarch-Heiberg manoeuvre. The radiological study of Nandi and his colleagues [3] defined the effect of anaesthesia on the profile of the pharynx, but gave no indication of the reasons why these additional manoeuvres should be required to ensure a clear airway after insertion of a Guedel airway. We have therefore undertaken a study to find out the exact site of obstruction when the Guedel airway is *in situ*, and to see the effect of further manipulations.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and consent was obtained from 22 male patients studied. All were aged between 63 and 84 yr and mean weight 72.6 kg (range 60-91 kg) presenting for routine urological procedures under general anaesthesia. None had apparent anatomical abnormalities of the upper airways or symptoms of any pathology in this area. All were ASA grades I and II and had no significant lung pathology. Premedication was prescribed at the discretion of the anaesthetist.

Lateral soft tissue radiographs of the pharynx were taken in the anaesthetic room at the time of induction of anaesthesia. The patients were supine, with the head in a neutral position, 3-4 cm above the plane of the table, using a ring support.

The Guedel airway was described in 1937 [1, 2] and is in daily use as a means of clearing a partly obstructed airway. It has always been assumed that its effectiveness depends on its ability to hold the tongue away from the back of the pharynx, thus providing a clear channel for respired gases. However, in a significant percentage of patients, further manoeuvres are required in order to

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The first radiograph was taken before induction and was an expiratory film, taken with the patient breathing through his nose. Anaesthesia was induced using thiopentone 3–4 mg kg⁻¹, and the second radiograph was taken during the brief apnoeic period. Anaesthesia was maintained with 50% nitrous oxide and enflurane in oxygen, with the patient breathing spontaneously via a face mask. The airway was maintained during this phase by dorsiflexion of the atlanto-occipital joint, jaw protrusion, or both, as necessary. When anaesthesia was considered to be deep enough by conventional means, a No. 4 Guedel airway (Portex Ltd, ref 100/303/040) was inserted, with the flange resting against the lips. Support of the jaw was then discontinued for a period not exceeding 7 s and the next radiograph was taken immediately, after allowing the head to fall back into a neutral position. Positioning was confirmed by inspection from the side. A further x-ray was taken with the head held in an extended position, by pulling the symphysis menti in an anterocephalic direction. The final radiograph showed the head held in a full Esmarch-Heiberg manoeuvre. This involves dorsiflexion at the atlanto-occipital joint and protruding the mandible anteriorly by exerting an anterior thrust behind the rami [4]. This was achieved with a specially constructed radiolucent Perspex device to prevent the anaesthetist's fingers obscuring the radiograph.

While the x-rays were being taken, periods of partial and complete obstruction were not allowed to continue for more than 7 s. With an inspired oxygen concentration of 50%, the alveolar PO_2 does not decrease to less than normal values under these circumstances.

All radiographs were taken on a Dean 38 mobile x-ray machine (Dean GEC X-ray Operators Ltd, Wembley). The exposure factors were in the range 62–65 kV (peak) and 12–16 mA s, depending on the patient's build. The exposure times were 60 ms and the film focal distance was 150 cm, with the patient midline 26 cm from the film.

A clinical assessment was made of the degree of airway obstruction present at the time of each radiograph. Three grades of ventilatory obstruction were used: clear, partially obstructed and totally obstructed. The airway was classified as clear if there were no adventitious sounds, the reservoir bag moved with ventilation and the chest moved in phase with the abdomen. Partial obstruction was noted if the reservoir bag moved

with ventilation but adventitious sounds were present, or there was evidence of indrawing of the suprasternal space, or the thorax moved out of phase with the abdomen. An airway was considered to be totally obstructed if there was no movement of the reservoir bag.

RESULTS

For technical reasons, satisfactory films during apnoea after induction of anaesthesia were obtained only in the last 17 patients. In these patients, induction of anaesthesia to the point of apnoea and before the onset of attempted breathing or the insertion of the Guedel airway, resulted in the changes listed in table I. The nasopharynx closed (A) in all but two patients. The antero-posterior dimension of the oropharynx (B) was highly significantly reduced, but became zero in only one patient. The epiglottis moved (C) posteriorly ($P = 0.014$) and appeared to touch the posterior pharyngeal wall in 10 of 17 patients.

Overall, only six of the 22 patients had an airway that was radiologically and clinically clear with the Guedel airway in place in the neutral head position. This increased to 16 radiologically clear and 19 clinically clear with dorsiflexion at the atlanto-occipital joint. With the full Esmarch-Heiberg manoeuvre, 15 were radiologically clear, but 21 were clinically clear (table II). There were 12 cases of total obstruction clinically in the neutral position, but none at all with dorsiflexion at the atlanto-occipital joint or the Esmarch-Heiberg manoeuvre.

Taking all 66 x-rays in the 22 patients, there was only one instance of partial and none of total clinical obstruction without apparent radiological cause (table III). There were, however, 10

TABLE I. Mean (SD) changes (mm) in some dimensions of the pharynx after induction of anaesthesia. A = Minimal distance from posterior pharyngeal wall to posterior aspect of soft palate. B = Minimal distance from posterior pharyngeal wall to base of tongue. C = Minimal distance from posterior pharyngeal wall to epiglottis. $n = 17$. (Compare with Nandi [3])

	Awake	Anaesthesia	P	Values of zero during anaesthesia (No.)
A	3.1 (2.4)	0.2 (0.8)	0.0003	15
B	11.0 (5.5)	3.9 (3.1)	0.0002	1
C	4.4 (4.1)	1.4 (2.6)	0.014	10

TABLE II. *Patency of the airway in three positions of the head*

No. of patients	Head in neutral position		Neck extended		Esmarch-Heiberg manoeuvre	
	X-ray appearance	Clinical airway patency	X-ray appearance	Clinical airway patency	X-ray appearance	Clinical airway patency
6	Clear	Clear	Clear	Clear	Clear	Clear
9	End of Guedel obstructed by tongue	Partially obstructed (2) Totally obstructed (7)	Clear Clear Clear (4)	Clear Clear Clear	Clear Clear Clear (2)	Clear Clear Clear
			Guedel apparently obstructed by epiglottis (1)	Clear	Guedel apparently obstructed by epiglottis (1)	Clear
			Obstructed by tongue (1)	Partially obstructed	Guedel in vallecula (1)	Clear
			Clear (1)	Partially obstructed	Clear	Clear
4	Guedel in vallecula	Partially obstructed (1) Totally obstructed (3)	Guedel apparently obstructed by epiglottis (1) Clear (1)	Clear Clear	Guedel in vallecula Guedel apparently obstructed by epiglottis Clear	Clear Clear Clear
			Guedel apparently obstructed by epiglottis (1)	Clear	Guedel apparently obstructed by epiglottis	Clear
			Guedel in vallecula (1)	Clear	Guedel still in vallecula	Clear
3	Guedel apparently obstructed by epiglottis	Partially obstructed (1) Totally obstructed (1) Totally obstructed (1)	Clear (2) Guedel in vallecula	Clear Partially obstructed	Clear Guedel still in vallecula	Clear Partially obstructed

TABLE III. *Comparison of clinically and radiologically apparent obstruction*

	Apparent radiological obstruction; clinically clear	Radiological and clinical obstruction	Clinically obstructed; no apparent radiological cause	Clear clinically and radiologically
Obstruction by tongue	—	10	—	—
Guedel lying in vallecula	4	6	—	—
Epiglottis obstructing Guedel airway	6	3	—	—
No radiological cause for obstruction	—	—	1	36
Total	10	19	1	36

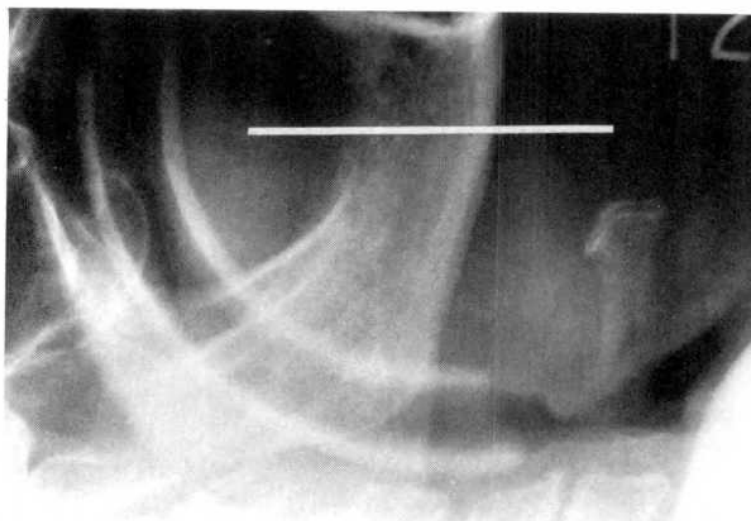


FIG. 1. A clear airway with the head in a neutral position. The tip of the epiglottis lies a few millimetres below the end of the Guedel airway. The bar represents 5 cm in the plane of the midline of the patient.

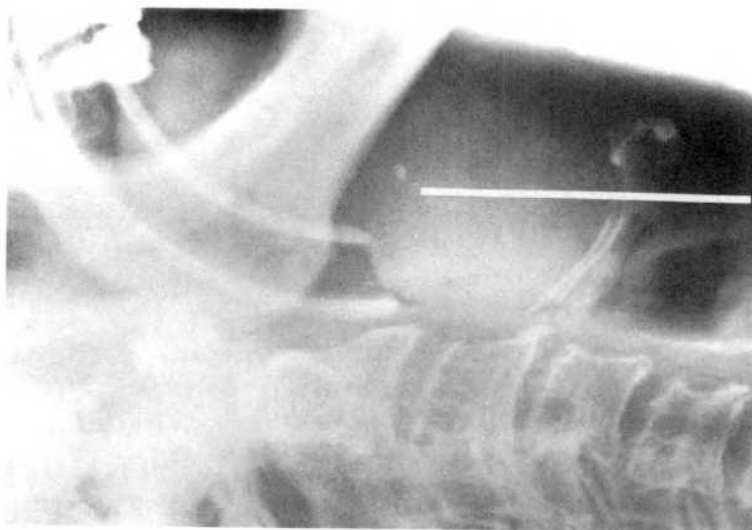


FIG. 2. Total obstruction of the Guedel airway by a "shelf" of tongue with the head in the neutral position. This appearance was always associated with clinical obstruction. The bar represents 5 cm in the plane of the midline of the patient.

instances of a clinically clear airway in the presence of an apparent radiological cause for obstruction. In four of these, the Guedel airway appeared to be lying in the vallecula and, in six patients, the epiglottis appeared to be obstructing the open end of the Guedel airway (table II). All the patients in whom the airway tip was shown to be lodged in the vallecula were older than 80 yr, and three of the four were edentulous. Otherwise, there was no relationship demonstrated between

the site of the airway tip and age or dentition. We had too few patients who were obese or very thin to draw any conclusions about the effect of body mass.

In six patients the airway was clear, both clinically and radiologically, with the Guedel airway in place and the head in the neutral position (fig. 1). The airway remained clear with both dorsiflexion at the atlanto-occipital joint and the Esmarch-Heiberg manoeuvre (table II).

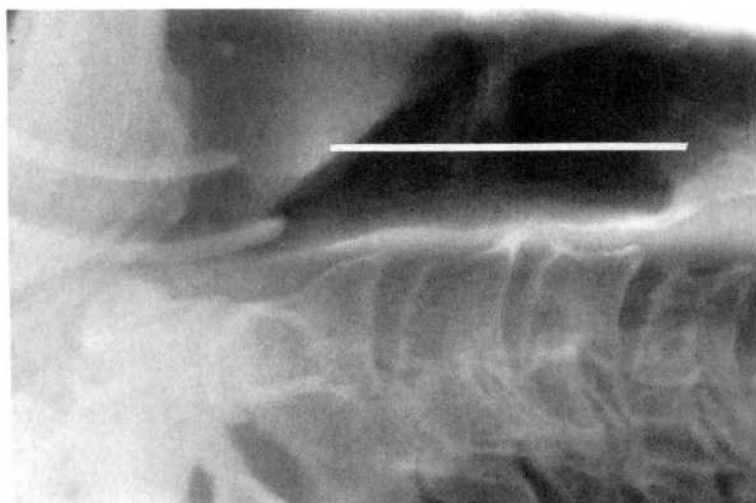


FIG. 3. The obstruction shown in Figure 2 has cleared by extension of the neck without protrusion of the jaw. Radiological clearing of the airway from this cause was always associated with a clinically clear airway. The bar represents 5 cm in the plane of the midline of the patient.



FIG. 4. The tip of the Guedel airway lies in the vallecula with total airway obstruction when the head is in the neutral position. The bar represents 5 cm in the plane of the midline of the patient.

In nine patients, the lower end of the Guedel airway was obstructed partially or totally when the head was in the neutral position, by a "shelf" of the posterior-inferior aspect of the tongue which was displaced by the Guedel airway itself (fig. 2). Clinically, this resulted in airway obstruction in all nine patients (complete in seven) (table II). In six of these patients the airway cleared, both clinically and radiologically, after the simple manoeuvre of dorsiflexion at the

atlanto-occipital joint (fig. 3). The airway was clinically clear in a seventh patient after dorsiflexion at the atlanto-occipital joint, but radiologically the epiglottis appeared to be impacted in the Guedel airway. The other two patients remained partly obstructed with dorsiflexion at the atlanto-occipital joint and, in one of these, the x-ray showed this was caused by the tongue. In the other patient there was no apparent cause for the partial obstruction.

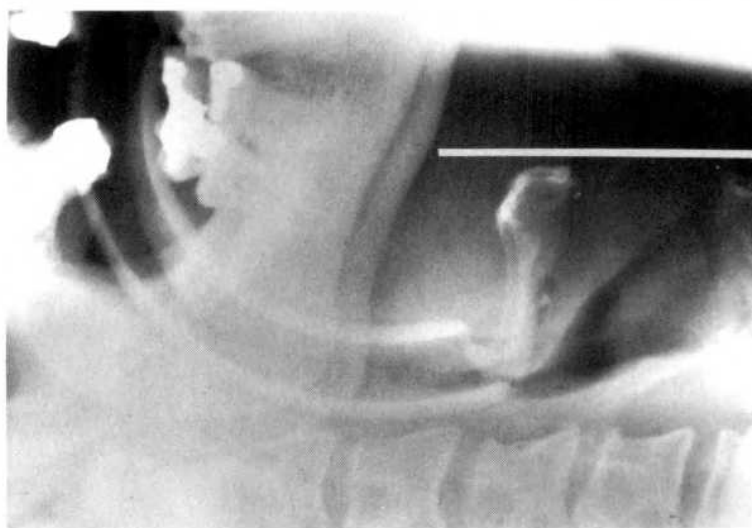


FIG. 5. Apparent obstruction of the end of the Guedel airway by the epiglottis. The bar represents 5 cm in the plane of the midline of the patient.

The full Esmarch-Heiberg manoeuvre resulted in a clinically clear airway in all nine of these patients, although one patient gave the radiological appearance of the tip of the epiglottis having moved against the tip of the Guedel airway. X-rays of two other patients showed the tip of the Guedel airway lying in the vallecula, which was not the case when the heads of these patients were in the neutral position or with dorsiflexion at the atlanto-occipital joint.

In four patients the radiograph showed the distal end of the Guedel airway to be lodged in the vallecula in the neutral position and, in each case, the airway was obstructed clinically, three of them totally (fig. 4). In one of these, the Guedel airway was dislodged by simple dorsiflexion at the atlanto-occipital joint, resulting in clinically unobstructed breathing. In another one, the Guedel airway remained in the vallecula, despite dorsiflexion at the atlanto-occipital joint and the Esmarch-Heiberg manoeuvre. Clinically, in this patient, the airway cleared on dorsiflexion at the atlanto-occipital joint, despite the radiographic appearance of the airway remaining in the vallecula. In the last two patients in this group, dorsiflexion at the atlanto-occipital joint gave the radiological appearance of the epiglottis moving into the end of the Guedel airway, and it remained there despite an Esmarch-Heiberg manoeuvre. In both of these patients, the airway was obstructed clinically in the neutral position, when the airway

was in the vallecula, but became clear on dorsiflexion at the atlanto-occipital joint, despite the x-ray appearances of the epiglottis still obstructing the airway.

The final group comprised three patients in whom the tip of the epiglottis appeared to be obstructing the end of the airway in the neutral position (fig. 5). Clinically, this caused total obstruction in two patients, but only partial obstruction in the third. Two of these airways were cleared completely by dorsiflexion at the atlanto-occipital joint, but in the third patient the Guedel airway slipped into the vallecula on extension of the head, and remained there, despite a full Esmarch-Heiberg manoeuvre. This was the only patient in our series whose airway remained partially obstructed, in spite of an Esmarch-Heiberg manoeuvre.

DISCUSSION

All anaesthetists are aware that, as anaesthesia deepens, upper airway obstruction occurs in several patients. Guedel believed this to be a result of the lower jaw falling backward, allowing the base of the tongue to lie against the posterior wall of the pharynx [1]. Several devices were designed to overcome this problem [2]; the Guedel airway is used most commonly today.

It has been shown recently by Nandi and his co-workers [3] that, after induction of anaesthesia,

there are significant approximations of the soft palate, tongue base and epiglottis to the posterior pharyngeal wall. In Nandi's study, the tongue base was not shown to touch the posterior pharyngeal wall. In the present study, changes in the dimensions of the pharynx during apnoea after induction of anaesthesia in the last 17 patients (table I) were substantially the same as those reported previously, and in only one patient did the tongue touch the posterior pharyngeal wall. Therefore the Guedel airway might be expected to be successful by providing an alternative route for airflow via the mouth instead of the nose. In practice, however, manoeuvres are often needed, such as dorsiflexion at the atlanto-occipital joint or an Esmarch-Heiberg manoeuvre, while in a small number of patients, obstruction may continue despite all attempts to overcome it.

This study has demonstrated at least three possible sites of obstruction of the Guedel airway: a "shelf" of tongue occluding the end of the Guedel airway; lodging of the airway in the vallecula; and obstruction by the epiglottis, perhaps with entry of the epiglottis into the airway. One cause of obstruction may change to another during attempts to clear the airway. We found only one case of upper airway obstruction when the cause was not apparent on x-ray. Conversely, we had several cases when the airway was clinically clear, but the radiological appearance showed a possible site of obstruction. This is presumably a result of superimposition of structures on the x-ray with lateral channelling of airflow around the obstruction, as we were only

taking a view in one plane. This is particularly relevant in patients in whom the epiglottis appears to be causing obstruction (fig. 5). Neither individual pharyngeal dimensions nor their changes after induction of anaesthesia showed any relationship to the type of airway obstruction resulting from the use of the Guedel airway.

Thus it is apparent that the failure of the Guedel airway to overcome obstruction is not a result of a single cause. There is no way of predicting the site of obstruction from clinical observation and efforts to overcome it may change the site of the problem rather than removing it. Further modification is made difficult by the multiplicity of problem sites. It is not easy to see how the Guedel airway may be altered to achieve the ideal of a "hands off" airway. Perforating the Guedel airway at a number of sites may allow the passage of gas to circumvent a site of obstruction, but this has been tried without success.

ACKNOWLEDGEMENT

The radiolucent device to undertake the Esmarch-Heiberg manoeuvre was made by Mr Maurice Tate.

REFERENCES

1. Guedel AE. *Inhalation Anaesthesia. A Fundamental Guide*. New York: The Macmillan Company, 1937; 105-106.
2. Minnitt RJ, Gillies J. *Textbook of Anaesthetics*, 7th Edn. Edinburgh: E. & S. Livingstone Ltd, 1948; 30-31.
3. Nandi PR, Charlesworth CH, Taylor SJ, Nunn JF, Doré CJ. The effect of general anaesthesia on the pharynx. *British Journal of Anaesthesia* 1991; 66: 157-162.
4. Heiberg J. A new expedient in administering chloroform. *Medical Times and Gazette* 1874; (January 10): 36.

CHANGES IN AMPLITUDE AND LATENCY OF THE P300 COMPONENT OF THE AUDITORY EVOKED POTENTIAL WITH SEDATIVE AND ANAESTHETIC CONCENTRATIONS OF NITROUS OXIDE†

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SUMMARY

The P300 component of the auditory evoked response was recorded from six subjects whilst they listened via headphones to a series of clicks which were interrupted unpredictably by a tone burst. They were instructed to press a button as quickly as possible after hearing the tone whilst breathing first air and then a series of increasing concentrations of nitrous oxide. Both the amplitude and the latency of the P300 changed in a dose-dependent manner with nitrous oxide, as did minimum reaction time. At nitrous oxide concentrations which prevented recall of any events that occurred whilst breathing the gas, four subjects continued to respond to the tone by pressing the button. In three subjects, the P300 wave was still detectable with a nitrous oxide concentration at which the task was no longer performed. These results show that there is retention of the ability to perform a reaction time task when there is a complete loss of recall of the task. There may be some recognition of an auditory stimulus, as manifest by a P300 wave, albeit reduced greatly in amplitude, in the absence of a motor response to it. The P300, therefore, merits investigation as a tool for studying conscious awareness under anaesthesia.

KEY WORDS

Anaesthetics, gases: nitrous oxide. Brain: auditory evoked potential. Memory: recall.

The widespread use of light anaesthesia in conjunction with neuromuscular block produces the potential for patients to be awake but unable

to communicate this state to the anaesthetist. However, there is still no reliable method of assessing if an apparently anaesthetized patient is awake or not, and further research is needed to study the interface between the conscious and the unconscious state.

Several methods have been evaluated during surgical anaesthesia and, of these, both the isolated forearm technique and the recording of auditory evoked potentials give some information about various stages of awareness [1]. The isolated forearm technique [2] attempts to detect conscious awareness directly by eliciting specific hand movements on command. Whilst the ability to obey a command under anaesthesia must carry a high risk of conscious awareness, the converse is not true, and it may underestimate the true incidence of awareness [3]. Furthermore, there are technical difficulties with prolonged or repeated occlusion of the limb and with arm movements interfering with the surgical field.

The early cortical components (25-100 ms) of the auditory evoked response show dose-dependent changes in amplitude and latency that are independent of the anaesthetic agent and have been validated as an indicator of awareness against the isolated forearm technique [4]. However, the

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method does have disadvantages. First, the evoked potentials are small ($0.5 \mu\text{V}$) and it takes time to average out the signal from the background EEG. Second, interpretation of the averaged data requires some expertise. Third, these early cortical responses signal only the arrival of a sensory volley at the primary auditory cortex. While this is a pre-requisite for awareness to occur it does not, on its own, imply any form of cognitive processing. An apparently normal early cortical evoked potential may occur in the absence of any conscious awareness of the eliciting stimulus, and when conscious awareness does occur, it does so at an increased latency [5]. Furthermore, using the middle latency responses to predict awareness overestimated its true incidence as detected by the isolated forearm technique [4]. Thus there is no clear relationship between the middle latency responses and conscious awareness. However, later event-related potentials imply a degree of cognitive processing [6] and might, therefore, approximate more closely to a conscious awareness of the stimulus.

Such an event-related potential is the P300. This wave occurs when a regular stimulus is interrupted unpredictably, for example by missing out a stimulus or by replacing it with a different one. The P300 is large ($10\text{--}20 \mu\text{V}$) and has a peak latency of about 300 ms from the unpredictable stimulus. It has been studied with sleep [7], sedative drugs [8], nitrogen narcosis [9] and low doses of nitrous oxide, up to 40% inspired [10–12]. It has also been studied during and after general anaesthesia with isoflurane [13]. This study describes the effect on the P300 in normal volunteers of breathing nitrous oxide to give end-tidal concentrations in the range 20–65%.

SUBJECTS AND METHODS

The study was performed in six anaesthetists who were healthy (ASA I) and of Senior Registrar or more senior status. Approval for the study was obtained from the local Ethics Committee.

Subjects were requested to fast for 5 h before the study and not to drive home afterwards. The subject was made comfortable lying on a bed and a 20-gauge i.v. cannula was placed in the dorsum of the left hand as a precautionary measure. Full resuscitation equipment was available and two anaesthetists (in addition to the subject) were present throughout all experiments.

P300 recordings

Clicks (1 ms duration) were presented to the subject via headphones at a rate of 1 s^{-1} . To elicit a P300 wave, one click was replaced periodically, in a pseudo-randomized fashion, by a tone burst (frequency 1.5 kHz, 100 ms duration) at an average frequency of 1 tone to 9 clicks. The subject was asked to concentrate on the clicks and to press a hand-held button as soon as the tone occurred. The EEG was recorded, using silver–silver chloride adhesive electrodes, from the vertex, referenced to linked ear lobes and with an earth electrode on the forehead. All inter electrode impedances were 2–3 k Ω . The EEG signal was amplified using an optically isolated amplifier and passed to a digital signal averager (NEC portable computer controlling a Cambridge Electronic Designs interface unit via CED SIGAV software). Sampling was triggered by the click preceding the tone and 3000 points were sampled over the next 3 s. The record thus showed the response not only to the tone, but also to the preceding and following clicks. Sixteen of these 3-s sweeps were collected and stored, and an average record formed from them using the SIGAV software. Sweeps contaminated by blinks or other large artefacts were rejected automatically using the amplitude-triggered sweep rejection option of the SIGAV program.

Reaction time recording

A second channel of the averaging system was used to record the time that the subject pressed the button in response to the tone. The shortest reaction time for each group of 16 samples was measured.

Nitrous oxide administration and monitoring

Throughout the experiment, the subject's oxygen saturation was monitored with a pulse oximeter (Ohmeda Biox 3700) via a finger probe. During nitrous oxide administration the subject's inspired and end-tidal concentrations of oxygen, carbon dioxide and nitrous oxide were monitored using a mini mass spectrometer (Ohmeda 6000). Mixtures of nitrous oxide and oxygen were delivered from a standard anaesthetic machine (Boyle International 2) via a Bain system to a mouthpiece. The subject wore a nose clip and supported the mouthpiece himself. The gas mixture was breathed until the end-tidal nitrous oxide concentration was stable and a P300 record-

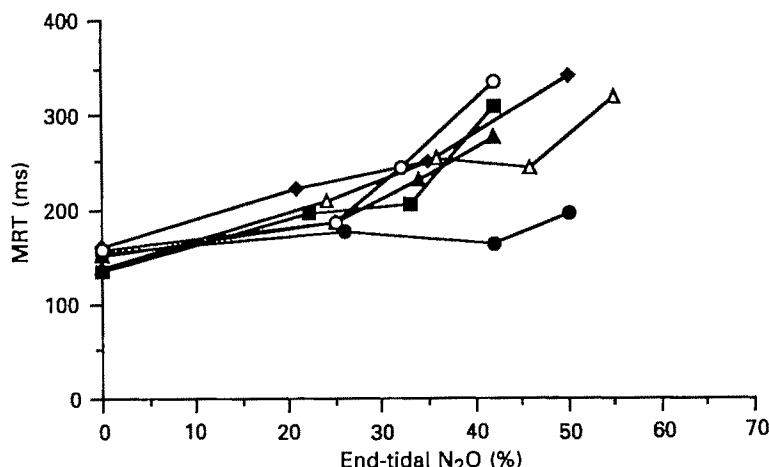


FIG. 1. Effect of end-tidal nitrous oxide (N_2O) concentration on minimum reaction time (MRT) for subjects Nos 1 (♦), 2 (△), 3 (●), 4 (○), 5 (■) and 6 (▲). $r = 0.78$; $P < 0.001$.

ing was performed. A recording was accomplished in all subjects with the end-tidal concentration of nitrous oxide changing by no more than 2–3%. The total gas flow was adjusted as necessary to keep the end-tidal carbon dioxide concentration in the range 4.5–5.5 kPa.

Experience and recall

At the end of each nitrous oxide study the subject was questioned about their mental experience and recall of events which had occurred during breathing the gas; for example hearing the tones, pressing the button and external disturbances such as alarms. Detailed records were kept of what each subject described.

Experimental programme

At the start of the experiment, two sets of recordings of the P300 and reaction times were obtained whilst the subject breathed air. The subject then breathed the first of the nitrous oxide/oxygen mixtures until the end-tidal concentration of nitrous oxide was stable when they were warned that a recording was about to start and reminded to press the button on hearing the tone. When the recordings of P300 and reaction times were complete the subject was allowed to recover whilst breathing room air. At the earliest possible opportunity they were questioned about recall as outlined above. When the end-tidal nitrous oxide concentration was $\leq 2\%$, the next concentration was administered. This sequence was repeated, increasing the inspired concen-

tration by 10% in each study until the subject no longer co-operated. Failure to keep still enough for EEG recording to be possible or failure to retain the mouthpiece were the usual reasons for terminating the experiment. A final recording was performed with the subject breathing air 15–20 min after nitrous oxide was discontinued. This programme represents a compromise between several conflicting requirements which are discussed later.

Statistics

Regression coefficients and intercepts were calculated using least squares linear regression analysis. All regression analysis was performed on the pooled data for all subjects (except for table II).

RESULTS

Behavioural changes with nitrous oxide

Of the seven subjects who originally volunteered for the study, one became very dysphoric at an end-tidal nitrous oxide concentration of 20% and was unable to co-operate with EEG recordings, so the experiment was abandoned. The results of the remaining six subjects are presented. Of these, subject No. 4 (symbol ○ in figures) also became dysphoric and unable to keep still enough to provide satisfactory EEG recordings at an end-tidal nitrous oxide concentration of 42%, although we managed to obtain a complete record of psychomotor measures. While breathing increased concentrations, the remaining five

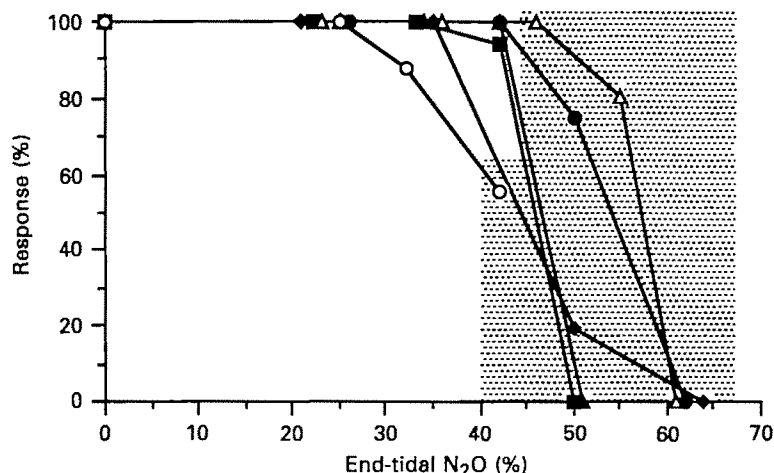


FIG. 2. Effect of nitrous oxide (N_2O) on the accuracy of performing the reaction task. 100% response = subject pressed on button in response to all 16 tones. All points in the shaded area represent responses made when the subject had no recall whatsoever of the recording period. Key to subjects as in figure 1.

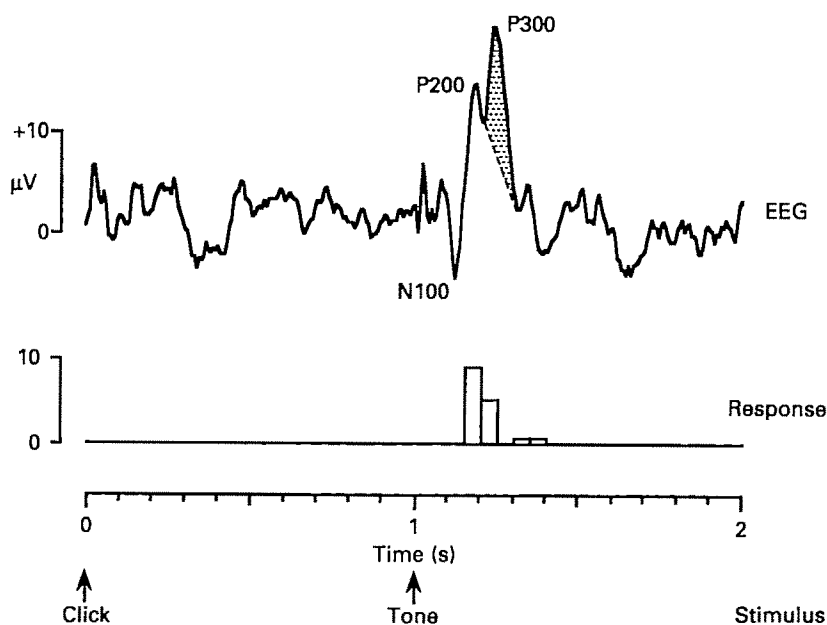


FIG. 3. Top trace: typical averaged EEG response to 16 stimuli in a subject breathing air. The principal components of the event related potential (N100, P200, P300) are indicated. The histogram depicts the distribution of the subject's reaction times to those stimuli. The timing of the tone and the preceding click are indicated.

subjects had experiences that were vivid and were described in terms of dissociation; for example, solving difficult problems with bizarre insights into the meaning of life. Despite these sensations, during which they were oblivious to the purpose of the study, they were able to co-operate with

and complete the experiment, although there was one other subject in whom we could perform psychomotor testing at an expired concentration of 62%, but EEG recordings were swamped by movement artefacts.

In common with other workers [10, 12], we

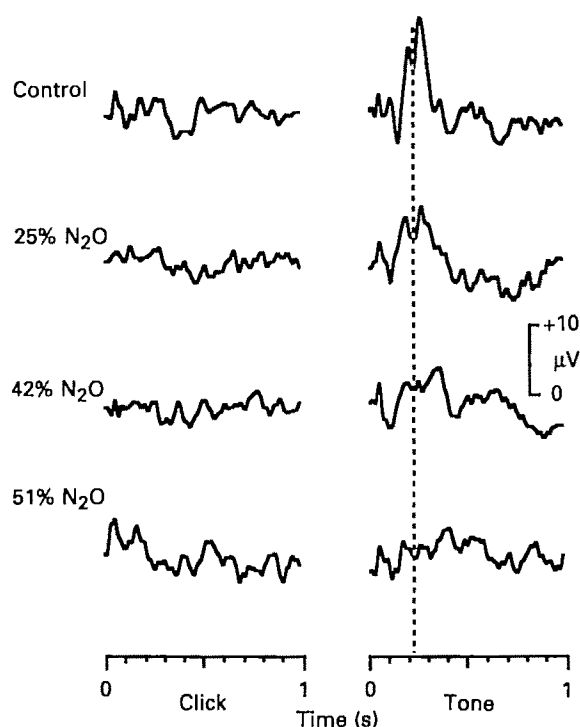


FIG. 4. Series of averaged EEG responses with increasing concentrations of nitrous oxide in one subject. Each trace is the average response to 16 stimuli. On the right are the responses to the tones and on the left, for comparison, are the averaged responses to the preceding click.

TABLE I. Calculated values of end-tidal nitrous oxide at which the P300 amplitude would be zero for each of the six subjects, as estimated by the intercepts on the nitrous oxide axis of the individual linear regression lines

	Subject No.					
	1	2	3	4	5	6
End-tidal N ₂ O (%)	66.4	69.3	56.6	36.4	69.5	62.0

found that the subjects' minimum reaction times increased with increasing nitrous oxide (fig. 1). Figure 2 shows how the subjects' accuracy at pressing the button in response to the tone altered with increasing nitrous oxide. At the lower concentrations, the subjects continued to respond to all the tones, albeit with a longer reaction time, but there was a fairly narrow range of concentrations over which the response decreased sharply.

Recall for the recording period was disrupted by lesser concentrations of nitrous oxide than affected the ability to respond. Four of the six subjects continued to respond to some of the tones by pressing the button with concentrations at which they could not recall any events that occurred whilst breathing the gas (points within the shaded area of figure 2).

Changes in the P300 with nitrous oxide

Figure 3 shows a typical averaged EEG response to a click and a tone and illustrates the

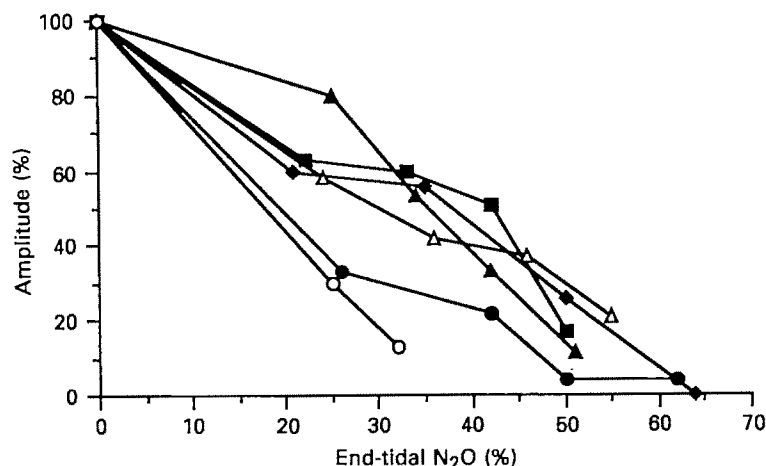


FIG. 5. Effect of nitrous oxide on P300 amplitude in each of the six subjects, normalized as a percentage of that subject's mean amplitude when breathing air at the beginning of the study. $r = -0.96$; $P < 0.0001$; X-intercept = 62%. Key to subjects as in figure 1.

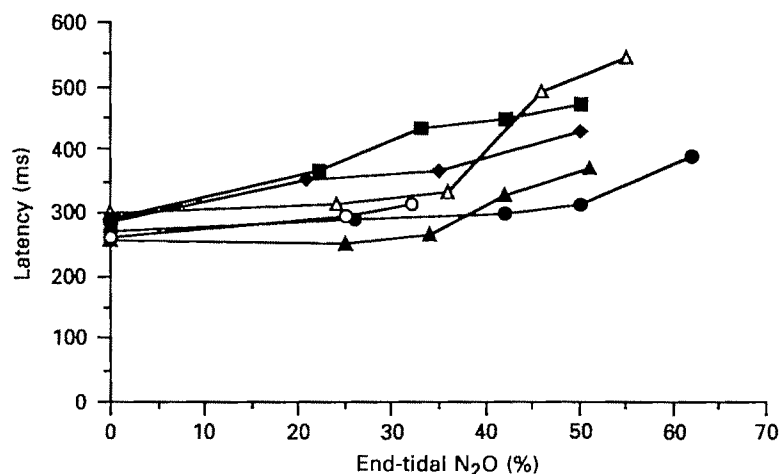


FIG. 6. Effect of nitrous oxide on P300 latency. $r = 0.67$; $P < 0.001$. Key to subjects as in figure 1.

temporal relationship between the motor response to the reaction task and the P300. The motor response was approximately 100 ms earlier than the peak P300 latency. The figure also illustrates the fact that, with our experimental paradigm, the P300 was seen on the falling phase of the P200 wave, which implies that simple measurements of peak amplitude are not appropriate. The method of measurement chosen was to draw a straight line to fit the decrease in P200 and to measure the area of the P300 above that line, as represented by the shaded area. A typical series of P300 records obtained from one subject breathing air and then increasing concentrations of nitrous oxide is shown in figure 4; as the nitrous oxide concentration increased, P300 became smaller and later.

Figure 5 shows how the amplitude of the P300 changed with increasing end-tidal concentrations of nitrous oxide. Because the absolute amplitude measurements in any one subject are influenced by such factors as electrode contact and position, it was necessary to normalize the measurements in order to compare them between subjects. Therefore, all amplitudes are given as a percentage of the mean P300 amplitude with the subject breathing air at the beginning of the study, for that subject.

All the subjects showed a step-wise decrease in P300 amplitude with increasing end-tidal concentration of nitrous oxide. The regression line calculated from the pooled data intercepts the x-axis at 62.3% nitrous oxide. This is at the top end of the range in which the subjects failed to push

the button, and well above the range in which recall was lost (fig. 2). It can be seen from the graphs that individuals differed in their sensitivities to nitrous oxide; the calculated nitrous oxide intercepts for each of the six subjects are shown in table I.

All subjects showed an increase in the peak latency of the P300 with increasing end-tidal concentrations of nitrous oxide (fig. 6). The relationship between the P300 amplitude and the performance of each of the subjects was similar to that between end-tidal nitrous oxide concentration and performance (fig. 7). At reductions in P300 amplitude less than 50% there was very little change in performance, but thereafter it decreased sharply.

Recovery from nitrous oxide

A final set of observations was obtained from five of the six subjects 15–20 min after they had finished breathing nitrous oxide (table II). Recovery was quite variable, but three of the five subjects had persistent changes in amplitude or latency of the P300 at this time, although the minimum reaction times are more or less normal. Note that the subject who was most sensitive to nitrous oxide (fig. 5) had the most attenuated P300 at this stage.

DISCUSSION

The results of this study have demonstrated that the P300 response of the auditory evoked potential to a randomly presented auditory event showed

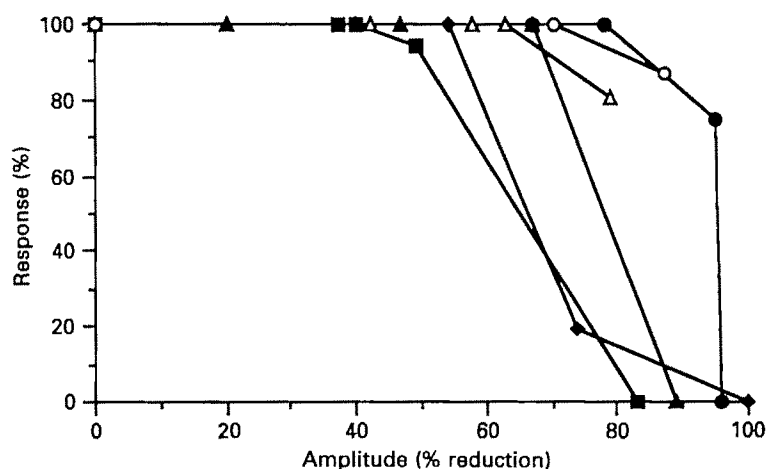


FIG. 7. P300 amplitude plotted against % response to the tones. There was negligible change in performance until the P300 was reduced to less than 50% of control.

dose-dependent changes in amplitude and latency over the range of end-tidal concentrations of nitrous oxide used in routine clinical practice. The calculated regression line for all the data showed that the amplitude of the P300 tended to zero at 62% end-tidal nitrous oxide. Four of the six subjects pressed a button in response to some or all of the tones at a stage when they had no recall of the proceedings and three of the subjects had a detectable P300 at a stage when they made no response at all to the tones. Thus the P300 seems to represent some residual processing of information in the absence of a motor response.

Two aspects of the methodology need to be discussed. First, the nitrous oxide concentrations were always presented to the subjects in ascending order. Whilst this is not ideal statistically, it proved impracticable to randomize the order. Table II illustrates the fact that the recovery of the P300 15 min after nitrous oxide was stopped varied between subjects. The intervals necessary

between trials in order to ensure zero carry-over from large to small concentrations would have made the experiment impossible to complete at one time. An alternative would have been to study different concentrations on different days, but that would have introduced new sources of variability such as electrode placings. The design chosen was a compromise, based on the assumption that any carry-over should have least effect from smaller to greater concentrations. Second, there is no standard method of measuring the amplitude of the P300. In our experiment it appeared on the falling phase of the P200 when air was breathed and gradually separated from this wave with increasing concentrations of nitrous oxide. This makes simple measurements of amplitude inappropriate because there is no suitable fixed point to which such measurements may be referred. The method used was to measure an area which approximated to the area of the response, and which underestimated the P300 the closer it was to the P200; that is, in this experiment it underestimated at smaller concentrations of nitrous oxide. Thus any errors from this source lessened, rather than enhanced, the dose-dependent changes in amplitude observed. It is then necessary to consider what these changes represent.

The P300 is maximal if the stimulus is infrequent and if its occurrence has some meaning to the subject, for example if he has been told beforehand that he has a task to perform when it occurs. In this situation the latency of the P300 is always longer than the associated reaction time

TABLE II. Recovery of P300 amplitude and latency and of minimum reaction time with the subjects breathing air 15–20 min after last breathing nitrous oxide. (Data for subject No. 2 were lost.)

Subject No.	P300 amplitude (% control)	P300 latency (change from control) (ms)	Reaction time (change from control) (ms)
1	84	+48	+16
3	107	–12	–22
4	37	+42	+13
5	91	–1	+2
6	68	–3	+21

[14], and so it is believed that the P300 reflects some part of the stimulus evaluation process, rather than the process of producing a motor response. Its latency may be too short for it fully to represent conscious awareness of the stimulus [5], but it represents a very much later stage in the pathway, just before consciousness, than do the early cortical components (about 50 ms) of the evoked potential. The fact that its amplitude tends to zero at 62% end-tidal nitrous oxide suggests that it is not useful as a measure of depth of anaesthesia, as it is not present throughout the range of anaesthetic concentrations usually used to perform surgery. However, we speculate that it might be used as a *marker for conscious awareness*. It is important to realize that it is not simply a marker for conscious awareness *with recall* because in all five subjects in whom satisfactory recordings could be obtained, it persisted at nitrous oxide concentrations with which recall of external events was lost. Some subjects were able to achieve a high degree of accuracy at pressing the button in response to the tones when they had no recall at all. This shows that lack of recall of events is a poor indicator of conscious awareness.

There is also an interesting relationship between the P300 amplitude and ability to respond to the tones. With the smaller concentrations of nitrous oxide, the reaction time lengthened gradually although the button was pushed in response to every tone. Then, at concentrations at which the P300 was already reduced by more than 50%, the response began to fail altogether. Although this failure was apparently abrupt, this is not really the case. There is, in effect, a continuum in which the reaction time gradually lengthens and then increases steeply to infinity. In parallel with this, the P300 gets progressively smaller and, in three of six subjects, it finally disappeared slightly after the motor response. No subject had a motor response to a tone in the absence of a P300. If we accept that the presence of a P300 represents some recognition of the tone, albeit attenuated and not recalled, then we have detected a state, in some subjects, in which the stimulus was recognized, but not acted upon. This implies that a change in the P300 may be used as a sensitive indicator of conscious awareness without recall, although we cannot prove this without more detailed psychometric testing.

We conclude that the P300 warrants further investigation as a tool for exploring the relationship between conscious awareness and anaesthesia.

REFERENCES

1. Jones JG. Foreword. In: Jones JG, ed. *Baillière's Clinical Anaesthesiology*, Vol. 3, *Depth of Anaesthesia*. London: Baillière Tindall, 1989; ix-xii.
2. Tunstall ME. Detecting wakefulness during general anaesthesia for Caesarean section. *British Medical Journal* 1977; 1: 1321.
3. Russell IF. Conscious awareness during general anaesthesia: relevance of autonomic signs and isolated arm movements as guides to depth of anaesthesia. In: Jones JG, ed. *Baillière's Clinical Anaesthesiology*, Vol. 3, *Depth of Anaesthesia*. London: Baillière Tindall, 1989; 511-531.
4. Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Doré CJ, Newton DEF, Jones JG. The auditory evoked response as an indicator of awareness. *British Journal of Anaesthesia* 1989; 63: 113-115.
5. Libet B, Wright EW, Feinstein B, Pearl DK. Subjective referral of the timing for a conscious sensory experience. A functional role for the somatosensory specific projection system. *Brain* 1979; 102: 193-224.
6. Sutton S, Tueting P, Zubin J. Information delivery and the sensory evoked potential. *Science* 1967; 155: 1436-1439.
7. Wesensten NJ, Badia P. The P300 component in sleep. *Physiology and Behaviour* 1988; 44: 215-220.
8. Samra KS, Bradshaw EG, Pandit SK, Papanicolaou AC, Barlett DM. The relation between lorazepam-induced auditory amnesia and auditory evoked potentials. *Anesthesia and Analgesia* 1988; 67: 526-533.
9. Fowler B, Pogue J, Porlier G. P300 latency indexes nitrogen narcosis. *Electroencephalography and Clinical Neurophysiology* 1990; 75: 221-229.
10. Fowler B, Kelso B, Landolt J, Porlier G. The effect of nitrous oxide on P300 and reaction time. *Electroencephalography and Clinical Neurophysiology* 1988; 69: 171-178.
11. Fenwick P, Bushman J, Howard R, Perry I, Gamble T. Contingent negative variation and evoked potential amplitude as a function of inspired nitrous oxide concentration. *Electroencephalography and Clinical Neurophysiology* 1979; 47: 473-482.
12. Estrin WJ, Moore P, Letz R, Wasch HH. The P300 event-related potential in experimental nitrous oxide exposure. *Clinical Pharmacology and Therapeutics* 1988; 43: 86-90.
13. Plourde G, Picton TW. Long-latency auditory evoked potentials during general anaesthesia. N1 and P3 components. *Anesthesia and Analgesia* 1991; 72: 342-350.
14. Ritter W, Simson R, Vaughan HG. Association cortex potentials and reaction time in auditory discrimination. *Electroencephalography and Clinical Neurophysiology* 1972; 33: 547-555.

EFFECTS OF I.V. LIGNOCAINE ON PSYCHOLOGICAL PERFORMANCE AND SUBJECTIVE STATE IN HEALTHY VOLUNTEERS

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SUMMARY

In order to assess the effects of different doses of lignocaine on performance, nine healthy volunteers aged 21-34 yr received i.v. infusions of saline, low and high dose lignocaine (mean plasma concentrations 0.92 and 1.78 $\mu\text{g ml}^{-1}$, respectively) in a double-blind randomized order. The Digit-Symbol Substitution Test (DSST) and Visual Analogue Scales (VAS) were performed repeatedly and a battery of performance tests once. The median (lower, upper quartile) number of correct responses for the DSST during the infusion period was: placebo 69 (67, 77); low 74 (71, 80); high 66 (61, 75) ($P < 0.001$, General Linear Models; all pairwise comparisons $P < 0.05$). None of the measures in the full battery showed any significant changes. VAS showed that subjects felt more interested ($P < 0.05$), drowsy ($P < 0.01$), dizzy, tense, abnormal, drunk and muzzy ($P < 0.001$) with lignocaine than with placebo. These results confirm that lignocaine can produce acute performance effects (both improvements and impairments). Subjects were clearly aware of the presence of lignocaine, suggesting that subjective reports may be a useful indicator of its CNS effects.

KEY WORDS

Anaesthetics, local: lignocaine. Psychological responses.

frequency [2]. In general, local anaesthetics lead to subjective reports of fatigue and dizziness [1-5].

The magnitude and duration of such effects is likely to be of concern in the selection of anaesthetic agents, particularly in day-case patients. In the study by Korttila [1], the mean peak plasma concentration after i.m. injection of plain lignocaine was 1.37 $\mu\text{g ml}^{-1}$, a concentration likely to be found, at least transiently, during regional anaesthesia [6].

It is difficult to assess the relationship between plasma concentrations and performance from this type of experiment. Only one dosage of each drug was used and the venous plasma concentration is an uncertain indicator of concentrations at the site of action when drug concentrations are changing, as occurs with single-dose studies.

An alternative is to use a continuous infusion of drug to obtain an approximate steady state [7-9]. This has several advantages. First, the arterio-venous artefact can be greatly reduced. Second, acute habituation effects may be detected. Third, a comprehensive test battery may be given with all tests being administered under similar drug conditions.

In the present experiment, subjective and objective effects of lignocaine were studied using infusions at two rates, calculated to achieve plasma concentrations of 1 and 2 $\mu\text{g ml}^{-1}$, in order to span

Several studies have shown that local anaesthetics may affect psychological performance and subjective state. Thus slowing of reaction times has been observed with lignocaine [1], while both bupivacaine and etidocaine caused an increase in reaction time, but a reduction in critical flicker

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the maximum concentration of $1.37 \mu\text{g ml}^{-1}$ obtained by Korttila [1].

SUBJECTS AND METHODS

We studied nine healthy male volunteers aged 21–34 yr (mean 28.4 yr) and weights 66–82 kg (mean 74.3 kg). No subject was taking any medication. All subjects gave written informed consent to the study, which was approved by the Ethics Committee of the Royal Infirmary, Edinburgh.

Subjects were given three treatments in random order: placebo (saline); low dose lignocaine (target placebo concentration $1 \mu\text{g ml}^{-1}$); high dose lignocaine (target $2 \mu\text{g ml}^{-1}$) (table I). At least 7 days elapsed between sessions. A short test battery was carried out at baseline and repeatedly during the infusion, while a more comprehensive battery designed to assess a broad range of CNS functions [10, 11] was performed once.

Digit-symbol substitution test. In this pencil-and-paper test, there was a key which matched nine symbols to the numbers 1–9. A series of random numbers was printed in a grid on the sheet and the subject wrote the corresponding symbol under each number, as quickly as possible. The numbers of correct and incorrect symbols written in 90 s were recorded [12].

Symbol-digit substitution test. In this automated version of the above test, subjects saw a key on a monitor screen which matched the nine symbols to the digits 1–9. A series of symbols appeared in a box below the key, one at a time, and the subject responded by pressing the appropriate number key as quickly as possible. The number of

correct and incorrect responses in 90 s was recorded.

Choice reaction time. This used an apparatus with a semicircular arrangement of six buttons with a light by each one. The subject initially placed his finger on a seventh button at the centre of the semicircle. At random intervals one of the lights was illuminated, and the subject responded by pressing the appropriate button as quickly as possible. The mean latency and total response time over 30 responses was recorded [13, 14].

Critical flicker fusion threshold. The subject observed a group of four lights which flickered at an increasing frequency. The subject responded when the lights appeared to be steady. The test was repeated with the frequency decreasing, the subject responding when flicker appeared to begin. The mean frequency of three observations in each direction was taken as the threshold [13].

Continuous attention task. A series of geometric patterns was flashed on a monitor screen, each pattern being shown for 0.1 s, the interval between patterns being 1.5–2.5 s. The subject's task was to respond whenever two consecutive patterns were the same. A total of 240 presentations, with 40 repetitions, was used on each occasion [10, 11]. The total number of errors (both false-positive and false-negative) was recorded, and the error index calculated [15].

Block pattern recognition test. A series of geometric patterns, as used in the continuous attention task, was displayed on a monitor screen, each followed, after a short interval—the viewing time—by a random pattern of much smaller black and white squares, which remained on the screen for 1 s. This second pattern acted as a backward mask, preventing further visual processing of the original stimulus. Two seconds after the onset of the original stimulus, four patterns appeared on the screen, and the subject responded by pressing a button corresponding to the stimulus pattern. Viewing times of 20–100 ms and an unmasked condition were used.

Sternberg memory scanning test. The subject was required to memorize a set of 1, 3 or 5 digits presented on the monitor screen. A series of digits was then shown on the screen, and for each digit the subject pressed a YES button if the digit was in the initial set, a NO button otherwise. The reaction

TABLE I. Treatment orders for individual subjects. Pl = placebo; L1 = lignocaine low dose (target concentration $1 \mu\text{g ml}^{-1}$); L2 = lignocaine high dose (target concentration $2 \mu\text{g ml}^{-1}$)

Subject No.	Session I	Session II	Session III
1	Pl	L1	L2
2	L2	Pl	L1
3	L1	L2	Pl
4	Pl	L1	L2
5	L2	Pl	L1
6	L1	Pl	L2
7	L1	L2	Pl
8	Pl	L1	L2
9	L2	Pl	L1

times for the correct responses for each of the conditions was recorded [16]. Two presentations of series of 20 digits were made for each set size.

Inspection time. In this measure of processing speed, the subject was presented with two illuminated vertical lines, one longer than the other. This was followed by a mask, consisting of two long lines. The subject responded by pressing a left or right button corresponding to the longer line in the original display. The inspection time (the interval between onset of stimulus and onset of mask) was varied according to the PEST algorithm, an adaptive procedure which decreases viewing time when subjects perform accurately, and increases it when errors occur. A progressive decrease in the step size allows the algorithm to "home in" to the time necessary for 85 % correct recognition [17, 18].

Visual analogue scales. Subjective effects were measured using 10 visual analogue scales, the opposite ends of which were marked: alert—drowsy; steady—dizzy; bored—interested; calm—tense; well—ill; lethargic—energetic; pleasant—unpleasant; normal—abnormal; sober—drunk; and clearheaded—muzzy. Non-specific questioning was also used ("How do you feel at the moment?"), and any symptom or other item reported or observed was rated by the tester on a seven-point severity scale.

Choice reaction time and critical flicker fusion were measured using the Leeds Psychomotor Tester [13]. Other automated tests were administered using a BBC Master 128 microcomputer with a separate response box [10].

Procedures

Each subject first took part in a familiarization session in which all the tests in the battery were introduced and practised.

Subjects were instructed to abstain from alcohol during the 24 h preceding the test sessions, and from caffeine and tobacco on the days of the test sessions, until completion of all procedures.

In each of the main sessions, a cannula (18-gauge Venflon) was inserted into the antecubital fossa of the non-dominant arm, for blood sampling. A smaller cannula (21-gauge Venflon) was inserted into a vein on the dominant forearm and connected to the infusion pump with flexible nylon tubing. This was arranged to allow free movement of the arm. A tap was fitted into the

cannulae behind the shoulder. The pump and connections were positioned behind the subject so that he would not be aware of the starting time of the infusions. Administration was blind to the subject and to the experimenter responsible for administering the tests. Infusion solutions were prepared by a physician who also had medical responsibility for the subjects. The physician was not blinded.

Saline was infused initially, to allow the subjects to settle and for baseline testing to be carried out. After approximately 20 min the loading dose commenced and after a further 10 min the maintenance dose was started. At termination of the main infusion (approximately 1.5 h) saline was resumed. For the low dose lignocaine condition, the loading dose was 1.26 mg kg^{-1} , followed by a maintenance infusion of $13.2 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$. For high dose lignocaine, double these amounts were used. For the placebo condition, all infusions comprised saline, but syringes and pump rates were changed at the same times as for the active infusions.

A short test battery, consisting of digit-symbol substitution, symbol-digit substitution, and the visual analogue scales was performed at 10-min intervals during the initial saline infusion and during the first 30 min of the experimental infusion. The full battery was performed at 30–80 min, followed by the short battery. The experimental infusion was replaced by saline, and the short battery performed again at 10-min intervals for 30 min. During the whole test period, non-specific questioning was carried out at approximately 10-min intervals, except when tests were in progress.

Blood samples were obtained for measurement of plasma lignocaine concentrations, before the infusion, at 30, 60 and 90 min after commencement of the main infusion, and at 15 and 30 min during the final saline infusion. Plasma concentrations of lignocaine were measured by HPLC [19].

Statistical analysis

The main outcome measures used were the mean scores for the items in the short test battery over the active infusion period. The difference between the scores at 30 and 90 min were assessed in order to test for acute tolerance effects, and the mean scores before active infusion commenced (baseline) and the final score (at 30 min after saline recommenced) were also analysed. These

TABLE II. Psychological performance as assessed by the main test battery during infusion of lignocaine. LQ = Lower quartile; UQ = upper quartile; RT = reaction time. No measure showed statistically significant differences between treatments ($P > 0.05$)

Measure	Placebo			Lignocaine low dose			Lignocaine high dose		
	Median	LQ	UQ	Median	LQ	UQ	Median	LQ	UQ
Choice reaction time									
Latency (ms)	382	345	430	363	329	425	367	335	462
Movement time (ms)	169	143	197	173	138	217	201	148	208
Total RT (ms)	576	483	601	503	461	633	569	516	663
Critical flicker fusion frequency									
Threshold (Hz)	30.2	28.8	31.4	28.6	28.3	29.5	30.5	28.5	30.9
Pattern recognition									
% correct 40–80 ms	51.7	48.3	56.7	58.3	51.7	61.7	50.0	40.0	53.3
% correct 100 ms	95	90	100	100	85	100	95	90	100
Continuous attention									
No. correct (/40)	36	35	38	36	31	38	38	35	39
No. incorrect (/40)	0	0	1	0	0	2	0	0	0.5
Error index	0.10	0.05	0.15	0.07	0.10	0.23	0.05	0.03	0.15
Memory scanning									
Mean RT (ms)	595	514	810	567	534	697	666	571	672
Inspection time									
IT85 (ms)	35	26	41	37	28	48	34	26	55

TABLE III. Effects of lignocaine on the short battery (mean scores over the period of the infusion). Med = Median; LQ = lower quartile; UQ = upper quartile. Statistical significance: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Pairwise comparisons: treatments not sharing a common underline significantly different ($P < 0.05$)

Measure	Placebo			Lignocaine low dose			Lignocaine high dose			Statistical significance	
	Med	LQ	UQ	Med	LQ	UQ	Med	LQ	UQ	P	Pairwise
Digit-symbol substitution											
No. correct (90 s)	69	67	77	74	71	80	66	61	75	***	<u>1 0 2</u>
Symbol-digit substitution											
No. correct (90 s)	55	46	61	57	46	59	51	47	56	ns	
Visual analogue scales											
Alert—Drowsy	13	9	21	29	20	35	36	21	53	**	<u>0 1 2</u>
Steady—Dizzy	5	2	10	19	16	34	42	36	57	***	<u>0 1 2</u>
Bored—Interested	39	28	50	41	35	53	61	47	74	*	<u>0 1 2</u>
Calm—Tense	6	2	8	13	8	16	28	20	38	***	<u>0 1 2</u>
Well—Ill	8	3	9	9	6	13	24	4	39	ns	
Lethargic—Energetic	48	43	56	41	34	61	40	34	65	ns	
Pleasant—Unpleasant	9	2	18	13	7	14	18	9	33	ns	
Normal—Abnormal	6	3	19	26	16	34	48	41	52	***	<u>0 1 2</u>
Sober—Drunk	3	2	9	19	5	30	37	29	53	***	<u>0 1 2</u>
Clearheaded—Muzzy	7	4	13	28	16	39	42	38	59	***	<u>0 1 2</u>

measures and the scores for the individual tests in the full test battery were analysed using General Linear Models applied to the ranked data set [20] to test for effects of treatment and session (order effect). Where significant treatment effects were found, pairwise comparisons were carried out. The level of significance was $P < 0.05$.

RESULTS

Data are presented by treatment for the full test battery in table II, and those for the short battery, including the subjective measures, in table III. Of the objective measures studied, only the digit-symbol substitution test showed statistically signif-

icant treatment effects ($P < 0.001$). All three pairwise comparisons were significant for this measure. The low dose of lignocaine was associated with an increase in the number of correct responses (improved performance) while the high dose led to a decrease (impairment).

The subjective measures (table III) showed clear effects of lignocaine. Seven of the 10 scales showed significant effects, with subjects feeling more interested ($P < 0.05$), drowsy ($P < 0.01$), dizzy, tense, abnormal, drunk and muzzy ($P < 0.001$). In most subjects these changes were clearly dose-related, with the effect of the low dose intermediate between that of the high dose and placebo.

No measure showed significant change between the 30-min and 90-min time points, and there were no differences between sessions at baseline. No statistically significant treatment effects were apparent 30 min after the end of the active infusion. Significant order effects were evident for pattern recognition (median (%) correct at 100 ms: session 1, 50; session 2, 52; session 3, 58); for the sober—drunk visual analogue scale (median position (mm): session 1, 9; session 2, 15; session 3, 33; the larger numbers indicate increasing feelings of drunkenness); and for the normal—abnormal visual analogue scale (median position (mm): session 1, 19; session 2, 19; session 3, 48; the larger numbers indicate increasing feelings of abnormality).

TABLE IV. Incidence of symptoms occurring during infusion, as elicited by non-specific questioning, and by observation. Each number represents the maximum severity, on a scale from 0 (absent) to 7 (very severe), reported for a single subject. Thus two subjects reported dizziness on high dose lignocaine, one with maximum severity 3, the other with maximum severity 4

	Placebo	Lignocaine low dose	Lignocaine high dose
Somnolence	2	5, 2, 3, 2, 3, 2, 2	3, 3, 3, 2, 4, 3, 5
Paraesthesia	2	3, 3	2, 2, 3
Tinnitus		2	2, 2, 2, 3
Dizziness		3, 2, 2	3, 4
Unpleasant/unusual taste		2, 2	2, 3
Muzziness			4, 2, 2
Intoxicated	2		4
Slurred speech	3		2
Nausea			4
Pain	3		
Cold	2		
Lightheaded			2
Hyperaesthesia			2
Dry mouth	2		

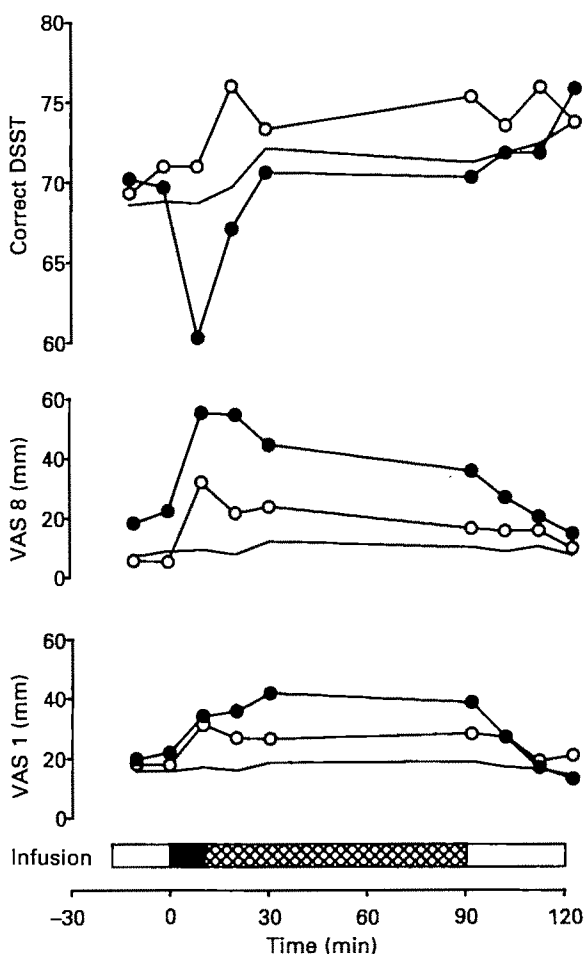


FIG. 1. Time course of effects (mean values) of lignocaine on digit-symbol substitution (DSST) and visual analogue scales Alert—Drowsy (VAS 1) and Normal—Abnormal (VAS 8). ● = High dose; ○ = low dose; — = placebo. Infusion: open bar = saline; black = loading dose; hatched = maintenance dose.

The time course of the effect of lignocaine is shown in figure 1. The effects on digit-symbol substitution and abnormal feelings appeared to peak during the loading dose, while drowsiness was more constant during the active infusion period.

Lignocaine was clearly associated with somnolence (tired, drowsy or sleepy), and there were more reports of paraesthesia, tinnitus, dizziness, taste in mouth and muzziness with lignocaine than with placebo (table IV).

Mean plasma concentrations of lignocaine over the three time points were in the range 0.75–1.16 $\mu\text{g ml}^{-1}$ for the low dose session (mean

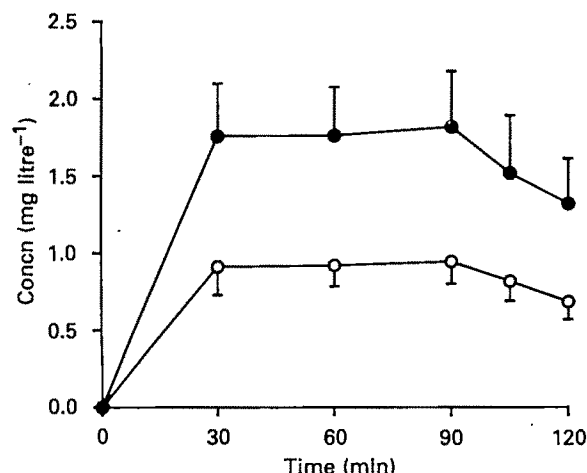


FIG. 2. Mean (SD) plasma concentrations of lignocaine during the infusion. ● = High dose (target $2 \mu\text{g mg}^{-1}$); ○ = low dose (target $1 \mu\text{g mg}^{-1}$).

$0.92 \mu\text{g ml}^{-1}$) and $1.4\text{--}2.35 \mu\text{g ml}^{-1}$ for the high dose (mean $1.78 \mu\text{g ml}^{-1}$) (fig. 2).

DISCUSSION

These results are in general agreement with the previous findings of Korttila [1], notably that lignocaine affected performance at concentrations likely to be found in clinical use. However, the effect was confined to a single objective test measure, the digit-symbol substitution test. The most striking finding was that with the smaller dose of lignocaine used there was a significant improvement in performance on this test, while with the greater dose, impairment occurred. Although a substantial number of statistical tests were performed in the present study, this is unlikely to be a chance finding for two reasons. First, the summary measures from the short battery were identified as primary measures in advance of the analysis. Second, the level of significance was such that, even if correction for multiplicity were considered appropriate, a significant result would still be found.

It is of interest that digit-symbol substitution showed effects of lignocaine, while the similar symbol-digit task was not affected significantly. The most obvious difference between the two tasks is that the latter is automated, but another aspect is pacing. The pencil-and-paper digit-symbol task is paced by the subject, while the automatic symbol-digit task is paced automatically by the computer. Moreover, there is no

possibility of the subject looking ahead in the latter task. These factors may substantially alter the nature of the task [21].

The mechanism of the biphasic response is unclear. Several studies have suggested that performance improvements may occur with small doses of CNS depressants such as benzodiazepines [22]. These results are usually interpreted in terms of anxiolytic or relaxant effects. Such effects seem unlikely here, in view of the dose-related increase in tension seen with the visual analogue scales.

Korttila's results for plain lignocaine showed only impairments, again only with a single measure (cumulative reaction time test). However, with other local anaesthetics, improvements occurred in some measures [2], but no effects in others [23]. As all these studies used single doses of local anaesthetics, it is not clear if these findings indicate differences between drugs, or if they are the result of assessing different parts of basically similar dose-response curves.

In contrast with the objective effects of lignocaine, subjective effects were apparent on a broad range of measures, with an obvious dose-response relationship. Subjects clearly felt the effects of both doses of the drug, the greatest effects being on the normal-abnormal and clearheaded-muzzy scales. There was no significant effect on the pleasant-unpleasant scale, although there was a slight trend towards the unpleasant end. Although the effect on the alert-drowsy scale was less marked than on abnormal or muzzy feelings, there was a clear indication of drowsiness, and this was apparent also from non-specific questioning.

The occurrence of order effects with objective measures is likely to reflect the effects of practice on task performance. Thus the improvement in performance with pattern recognition tasks suggests that the initial practice session may have been inadequate. The statistical method used is valid in the presence of order effects, but some loss of power may occur. Practice appears to have been sufficient for the other measures.

Several of the measures, for example digit-symbol substitution and normal-abnormal VAS, show a peak effect 10-20 min after commencement of the infusion, with the effect decreasing rapidly (although not returning to placebo levels). This is most likely to be caused by a peak of lignocaine concentration during loading, although rapid habituation cannot be excluded. However,

the latter explanation is made less likely by the fact that no significant difference was seen for any measure between 30 and 90 min.

The steady state phase of this experiment should resemble conditions during recovery from the effects of local anaesthetics. There is evidence for impairment at a plasma concentration of lignocaine around $1.5\text{--}2\text{ }\mu\text{g mg}^{-1}$, but not at half this concentration. Thus it would seem unlikely that concentrations of $1\text{ }\mu\text{g mg}^{-1}$ or less would be associated with significant impairment. Moreover, the fact that the subjective effects were clearly evident at smaller concentrations than caused impairment, suggests that simply questioning patients should be a useful index of recovery. These hypotheses, however, need to be tested in patients recovering from such procedures and, preferably, compared with recovery from the effects of general anaesthetics.

REFERENCES

- Korttila K. Psychomotor skills related to driving after intramuscular lidocaine. *Acta Anaesthesiologica Scandinavica* 1974; 18: 290-296.
- Korttila K, Hakkinen S, Linnoila M. Side effects and skills related to driving after intramuscular administration of bupivacaine and etidocaine. *Acta Anaesthesiologica Scandinavica* 1975; 19: 384-391.
- Scott DB. Evaluation of clinical tolerance of local anaesthetic agents. *British Journal of Anaesthesia* 1975; 47: 328-331.
- Scott DB. Evaluation of the toxicity of local anaesthetic agents in man. *British Journal of Anaesthesia* 1975; 47: 56-61.
- Scott DB. Toxicity caused by local anaesthetic drugs. *British Journal of Anaesthesia* 1981; 53: 553-554.
- Tucker GT, Mather LE. Properties, absorption, and disposition of local anaesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade*. Philadelphia: Lippincott, 1988; 47-110.
- Tiplady B, Fagan D, Lamont M, Bannister J, Brockway M, Scott DB. A comparison of the CNS effects of enprofylline and theophylline in healthy subjects assessed by performance testing and subjective measures. *British Journal of Clinical Pharmacology* 1990; 30: 55-61.
- Breimer DD, Jochemsen R, Kamphuisen HAC, Nicholson AN, Spencer MB, Stone BM. Central effects during the continuous osmotic infusion of a benzodiazepine (triazolam). *British Journal of Clinical Pharmacology* 1985; 19: 807-815.
- Kaplan HL, Sellers EM, Hamilton C, Naranjo CA, Dorian P. Is there acute tolerance to alcohol at steady state? *Journal of Studies on Alcohol* 1985; 46: 253-256.
- Tiplady B. An automated test battery for the detection of changes in mental function and psychomotor performance. *British Journal of Clinical Pharmacology* 1985; 20: 305P.
- Tiplady B. A continuous attention test for the assessment of the acute behavioral effects of drugs. *Psychopharmacology Bulletin* 1988; 24: 213-216.
- Wechsler D. *The Measurement and Appraisal of Human Intelligence*, 4th Edn. Baltimore: Williams and Wilkins, 1958.
- Hindmarch I. A 1,4-benzodiazepine, temazepam (K3917), its effect on some psychological parameters of sleep and behaviour. *Arzneimittel-Forschung* 1975; 25: 1836-1839.
- Frewer LJ, Hindmarch I. The effects of time of day, age, and anxiety on a choice reaction task. In: Hindmarch I, Aufdembrinke B, Ott H, eds. *Psychopharmacology and Reaction Time*. Chichester: Wiley, 1988; 103-114.
- Pigache RM. Comparison of scoring methods for tests of attention, including an error index for use with schizophrenic patients. *Perceptual and Motor Skills* 1976; 42: 243-253.
- Sternberg S. Memory scanning: new findings and current controversies. *Quarterly Journal of Experimental Psychology* 1975; 27: 1-32.
- Vickers D, Nettelbeck T, Willson RJ. Perceptual indices of performance: the measurement of 'inspection time' and 'noise' in the visual system. *Perception* 1972; 1: 263-295.
- Taylor MM, Creelman CD. PEST: Efficient estimates on probability functions. *Journal of the Acoustical Society of America* 1967; 41: 782-787.
- Nation RL, Peng GW, Chiou WL. H.P.L.C. method for simultaneous detection of lidocaine and its N-dealkylated metabolites in plasma. *Journal of Chromatography* 1979; 162: 466-473.
- Conover WJ. *Practical Nonparametric Statistics*, 2nd Edn. New York: John Wiley & Sons, 1980.
- Broadbent DE. Performance and its measurement. *British Journal of Clinical Pharmacology* 1984; 18: 5S-9S.
- Palva ES, Linnoila M, Saario I, Mattila MJ. Acute and subacute effects of diazepam on psychomotor skills: interaction with alcohol. *Acta Pharmacologica Toxicologica* 1979; 45: 257-264.
- Korttila K. Lack of impairment of skills related to driving after intramuscular administration of prilocaine or mepivacaine. *Acta Anaesthesiologica Scandinavica* 1977; 21: 31-36.

PROPOFOL AND MIDAZOLAM ACT SYNERGISTICALLY IN COMBINATION

T. G. SHORT AND P. T. CHUI

SUMMARY

We have studied interactions between i.v. propofol and midazolam for induction of anaesthesia in 200 unpremedicated female patients undergoing elective gynaecological surgery. Using end-points of "hypnosis" (loss of response to verbal command) and "anaesthesia" (loss of response to a 5-s transcutaneous tetanic stimulus), we determined dose-response curves for propofol and midazolam alone and in combination. For hypnosis, synergistic interaction was found ($P < 0.01$), the combination having 1.44 times the potency of the individual agents. Although midazolam failed to produce anaesthesia in the dose range used, the dose of propofol required to produce anaesthesia was reduced by 52% in the presence of midazolam ($P < 0.01$). The reduction in arterial pressure at induction was the same for the combination as for the individual agents. The cause of the synergism was not clear, but may have been interaction at CNS GABA_A receptors.

KEY WORDS

Anaesthetics, intravenous: propofol. Hypnotics, benzodiazepines: midazolam. Induction. Pharmacology: drug interactions.

Several i.v. agents, including thiopentone [1, 2], fentanyl [3] and alfentanil [4, 5] have been shown to act synergistically when given in combination with midazolam at induction of anaesthesia using the end-point of hypnosis (loss of response to verbal command) to define successful induction. The use of propofol in combination with midazolam has been studied also [6], but the nature of the sedative interactions is not known.

In this study we examined the interaction between propofol and midazolam when combined for induction of anaesthesia at two end-points that correspond to hypnosis and anaesthesia.

PATIENTS AND METHODS

After approval from the Research Ethics Committee of the Chinese University Faculty of Medicine, we studied 200 adult Chinese female patients who presented for elective gynaecological surgery and gave informed consent. Criteria for entry into the study were: age 18-40 yr, ASA grade I or II, no recent ingestion of psychotropic medication and weight within 20% of ideal. All patients were unpremedicated.

In the first part of the study, dose-response relationships were established for propofol and midazolam given individually. One hundred and twenty patients were allocated randomly to 12 groups of 10, each receiving one of seven doses of propofol (0.7, 1.0, 1.3, 1.6, 1.9, 2.2, 2.5 mg kg⁻¹) or one of five doses of midazolam (0.1, 0.125, 0.15, 0.175, 0.2 mg kg⁻¹). The midazolam doses were determined from previous work undertaken by one of the authors [1] and the propofol doses from a pilot study. All drugs were injected over 10 s into a forearm vein, followed by flush with 10 ml of physiological saline. The observer was blind to the dose given.

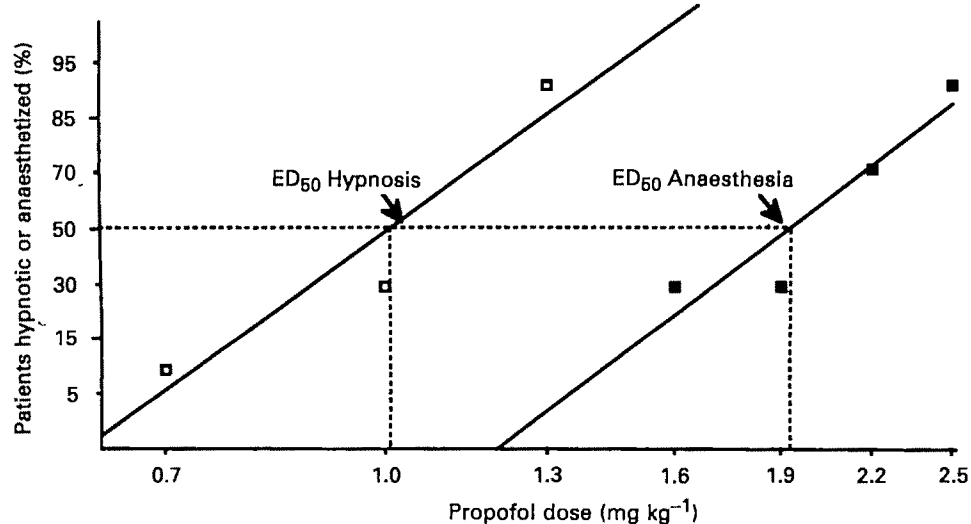
Patients were assessed for hypnosis and anaesthesia 2 min after propofol and 4 min after midazolam, these times being the approximate time to peak effect of each drug when given as an i.v. bolus. Hypnosis was assessed as failure to open the eyes on verbal command. In those patients who achieved hypnosis, anaesthesia was assessed as failure to respond to a standard 5-s transcutaneous tetanic stimulus (50-Hz, 80-mA, 0.25-ms pulses) over the ulnar nerve—an end-point shown to equate to MAC for volatile

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TABLE I. Proportions of patients achieving hypnosis and anaesthesia and mean (SD) decrease in mean arterial pressure (MAP) at 2 min, after each dose of propofol, midazolam or the combination

Drug dose (mg kg ⁻¹)		Proportion hypnotic	Proportion anaesthetized	Decrease in MAP (mm Hg)
Midazolam	Propofol			
0.1	0	0.2	0	14.7 (14.3)
0.125	0	0.3	0	18.0 (10.9)
0.15	0	0.5	0	12.5 (12.4)
0.175	0	0.8	0	10.9 (7.2)
0.2	0	0.8	0	10.0 (7.1)
0	0.7	0.1	0	12.7 (11.2)
0	1.0	0.3	0	11.9 (8.1)
0	1.3	0.9	0	10.9 (7.2)
0	1.6	1.0	0.3	16.7 (9.9)
0	1.9	1.0	0.3	12.0 (10.4)
0	2.2	1.0	0.7	7.3 (13.6)
0	2.5	1.0	0.9	12.5 (8.7)
0.03	0.21	0.2	0	6.8 (5.0)
0.04	0.29	0.4	0	11.8 (14.7)
0.05	0.36	0.5	0	10.4 (12.1)
0.065	0.46	0.8	0	11.6 (14.1)
0.085	0.60	1.0	0	16.8 (9.3)
0.10	0.71	1.0	0.1	20.3 (10.5)
0.13	0.92	1.0	0.4	17.0 (7.6)
0.17	1.2	1.0	0.9	15.5 (13.6)

Fig. 1. Hypnotic (□) and anaesthetic (■) (log)dose-(probit)response relationships for propofol. The ED₅₀ for hypnosis was 1.01 mg kg⁻¹ and that for anaesthesia 1.93 mg kg⁻¹.

anaesthetics [7]. Arterial pressure was recorded at 1-min intervals during the observation period, using an automated oscillometric arterial pressure recorder (Dinamap 1846SX, Critikon).

In the second part of the study, we examined propofol and midazolam given in combination.

Beginning with a combination of 50% of the ED₅₀ for hypnosis for each drug, we chose five doses smaller than this and two doses greater, whilst maintaining a constant dose ratio. The doses of propofol and midazolam, respectively, were 0.21/0.03, 0.29/0.04, 0.36/0.05, 0.46/0.065,

0.60/0.085, 0.71/0.10, 0.92/0.13 and 1.2/0.17 mg kg⁻¹. Midazolam was administered 2 min before propofol and a further 2 min was allowed before assessment, so that both drugs would be reaching peak effect at approximately the same time.

Statistical analysis was performed using analysis of variance to compare age, weight and arterial pressure measurements in patient groups. For graphical display and calculation of ED₅₀ values for hypnosis and anaesthesia the log(dose)-response curves were linearized using probit transformation [8]. When the proportion of patients achieving hypnosis or anaesthesia was 0 or 1.0, the data were excluded from subsequent analysis.

Interactions using the hypnotic end-point were examined by the method of Plummer and Short [9]. It is an extension, to the case of non-parallel log(dose)-response curves, of a method described by Finney in which the joint effects of drugs are compared under the hypotheses of additive effects and non-additive effects [8]. Proportions of patients who had achieved hypnosis with each treatment were converted to logits and the following additive model fitted to the data:

$$Y = \beta_0 + \beta_1 \log(T + (P \cdot M)) \quad (1)$$

where Y = logit transformed response; T = dose of propofol (mg kg⁻¹); M = dose of midazolam (mg kg⁻¹); P = relative potency at the appropriate effect level; β_0 and β_1 = variables to be estimated. By multiplying the dose by the relative potency, the former is converted into the "equivalent" dose of propofol; thus the term $T + (P \cdot M)$ may be thought of as "total propofol equivalents". Analogously, the term $M + (T/P)$ may be considered as "total midazolam equivalents" denoted by M_e , and is given by:

$$\log(P) = \beta_2 + \beta_3 \log(M_e) \quad (2)$$

where $M_e = M + (T/P)$.

The following model describing non-additive behaviour was also fitted to the data:

$$Y = \beta_0 + \beta_1 \log(T + P \cdot M + \beta_4 (T \cdot P \cdot M)^{0.5}) \quad (3)$$

where β_4 is analogous to Finney's coefficient of synergism.

Combinations of the drugs were considered to be non-additive if equation (3) fitted the data significantly better than equation (1).

The nature of the propofol-midazolam interaction for anaesthesia was examined by testing for

a horizontal shift in the propofol log(dose)-response curve in the presence of midazolam. For this, the proportions of patients anaesthetized at each dose were converted to logits, and log(dose)-logit(response) curves were fitted by weighted least squares using SPSS-X [10]. $P \leq 0.05$ was regarded as significant.

RESULTS

There were no significant differences in age or weight of patients among the three treatment groups. The mean ages of patients receiving midazolam, propofol and the combination respectively were 31.6, 30.5 and 30.5 yr and mean (SD) weights 51.0 (9.4), 50.3 (7.7) and 50.7 (8.3) kg. The proportions of patients that achieved hypnosis and anaesthesia after each dose of propofol and midazolam are listed in table I.

The propofol dose-response curves for hypnosis and anaesthesia are presented in figure 1. The ED₅₀ for hypnosis was 1.01 mg kg⁻¹ and that for anaesthesia 1.93 mg kg⁻¹. The midazolam dose-response curve for hypnosis is presented in figure 2. The ED₅₀ for hypnosis was 0.14 mg kg⁻¹. No patient became anaesthetized in the midazolam group with the doses used.

The dose-response curve for hypnosis using the combination of propofol and midazolam was compared with the dose-response curves for the two individual agents (fig. 3). The doses of propofol and propofol-midazolam combination were expressed as midazolam equivalents, in order that the curves for propofol and midazolam when used individually lay along the same line. The combination acted synergistically ($P < 0.01$), the coefficient of synergism being 0.78. This suggests that a dose of midazolam 0.1 mg kg⁻¹ combined with a hypnotically equi-effective dose of propofol (0.79 mg kg⁻¹) gave a response equivalent to midazolam 0.278 mg kg⁻¹ ($0.1 + 0.1 + 0.078 = 0.278$) rather than midazolam 0.2 mg kg⁻¹ as would be expected if the drugs were additive. Another way of expressing this is that, when the combination was used in equi-effective doses, 85 % of patients went to sleep using a total dose equivalent to that which put only 50 % of patients to sleep using each agent individually.

The dose-response curves of propofol and the midazolam-propofol combination for anaesthesia are shown in figure 4. The addition of midazolam shifted the curve to the left ($P < 0.01$). The dose of propofol required to anaesthetize 50 % of

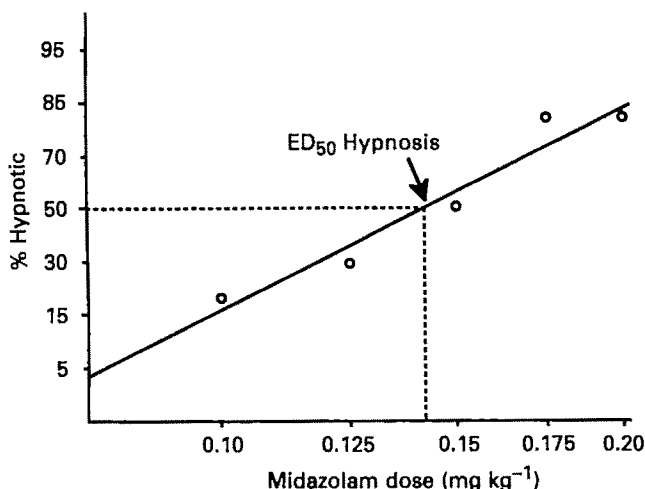


FIG. 2. Hypnotic (log)dose-(probit)response relationship for midazolam. The ED_{50} for hypnosis was 0.14 mg kg^{-1} . No patient achieved anaesthesia in the dose range used.

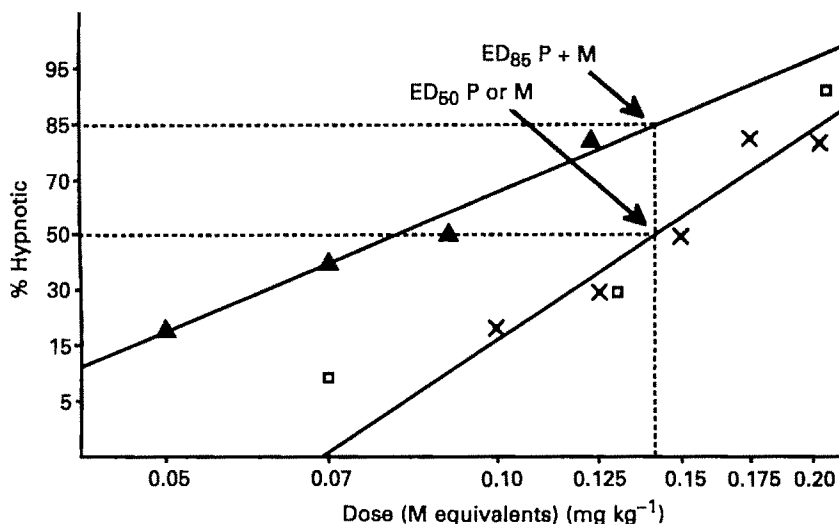


FIG. 3. (Log)dose-(probit)response curve for hypnosis of the propofol-midazolam (P+M) combination ($\blacktriangle$) compared with dose-response curves for the two individual agents ($\times$ = midazolam (M); $\square$ = propofol (P)). Doses of propofol and propofol-midazolam combination have been converted to "midazolam equivalents". The curve for the combination is shifted significantly to the left, indicating a synergistic interaction ($P < 0.01$). With the combination 85 % of patients achieved hypnosis using a total dose equivalent to that which achieved hypnosis in 50 % of patients using either agent individually.

patients was reduced from 1.93 mg kg^{-1} to 0.93 mg kg^{-1} , with the addition of midazolam 0.13 mg kg^{-1} at this point.

Arterial pressure measurements were analysed only up to the time of assessment of hypnosis and anaesthesia, because of the changes in arterial pressure caused by these assessments and the variable stimuli applied depending upon the degree of sedation. A decrease in systolic, diastolic

and mean arterial pressure occurred in all three treatment categories ($P < 0.01$), but there was no correlation between increasing dose and the magnitude of change in arterial pressure for midazolam, propofol or the combination. The maximum decrease in mean arterial pressure occurred at 2 min for all three treatments (table I). Comparing the three treatments at similar doses based on their hypnotic potency (proportion

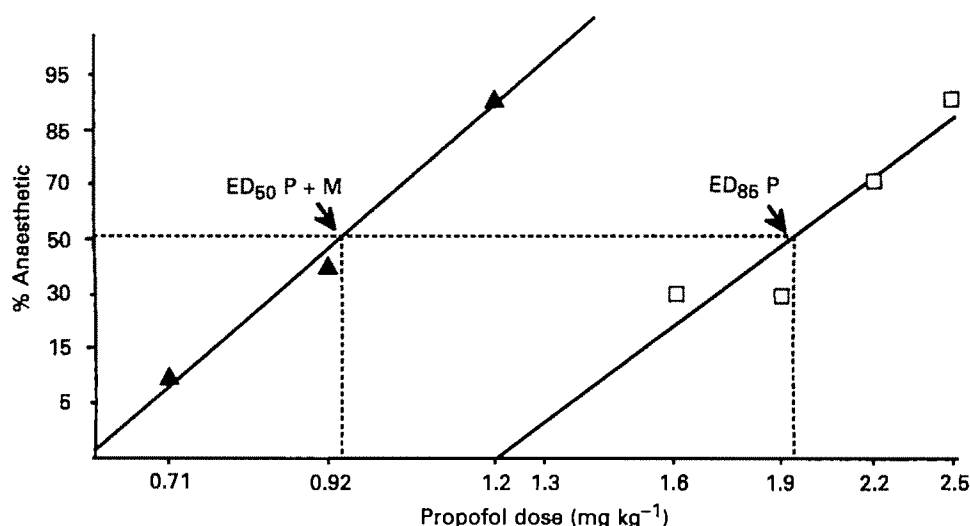


FIG. 4. Anaesthesia (log)dose-(probit)response curves of propofol (P) alone (□) and when combined with hypnotic doses of midazolam (P + M). (▲) The curve for the combination is shifted significantly to the left ($P < 0.001$). The addition of midazolam 0.13 mg kg^{-1} reduced the dose of propofol required to achieve anaesthesia in 50% of patients from 1.93 to 0.93 mg kg^{-1} .

hypnotic from 0.1 to 0.9) there were no differences in the decrease in arterial pressure among the three treatments. Comparing the changes in arterial pressure produced by propofol with the midazolam-propofol combination for anaesthesia on the same basis, there was again no difference between the two treatments.

DISCUSSION

The ED_{50} values for hypnosis of 1.01 mg kg^{-1} for propofol and 0.14 mg kg^{-1} for midazolam are comparable to previously reported values [1, 11–13]. There are no comparative data available for the end-point of anaesthesia as used in this study. With the combination, the coefficient of synergism was 0.87 , corresponding to an ED_{50} 44% less than that expected if the drugs were simply additive. Although we were unable to demonstrate any anaesthetic action of midazolam in the doses used, a dose approximately equal to its ED_{50} for hypnosis caused a 52% increase in the anaesthetic potency of propofol. Thus, in the presence of propofol, midazolam acted as an equi-effective anaesthetic agent.

These results parallel closely those found for thiopentone-midazolam combination reported previously. A similar shift in the dose-response curve for anaesthesia was observed and similar synergism found for hypnosis [1]. However, the

coefficient of synergism was larger in the present study: 0.87 , compared with 0.37 for thiopentone-midazolam.

The reasons for the synergism observed are not clear, as little is known about the mechanism by which propofol causes sedation and anaesthesia. In a comparative study of the effects of ketamine, alphaxalone-alphadolone, methohexitone and propofol on synaptic excitations and inhibitions in the spinal cords of decerebrate cats, propofol was found to increase amplitude and time course of dorsal root potentials (DRP) in a manner similar to, but to an extent less than, methohexitone and alphaxalone-alphadolone. Propofol also depressed polysynaptic reflexes in a manner similar to ketamine [14]. The potentiation of DRP is thought to be a GABA_A receptor mediated effect. It is not known what mechanism is involved with depression of polysynaptic reflexes, but this is an effect seen only weakly with barbiturates. Propofol has been shown also to potentiate duration of sleep and depth of anaesthesia in brain noradrenaline-depleted rat pups; this effect is also similar to that seen with barbiturates [15]. Although it has been postulated that these drugs produce an anaesthetic state via noradrenergic pathways, because there are GABA_A receptors present as inhibitory components on noradrenergic pathways it is possible that this effect is also a GABA_A receptor effect, reflecting GABA

predominance in the absence of significant nor-adrenergic discharge [16]. These studies provide circumstantial evidence of a role for GABA_A receptors in mediating sedation caused by propofol and suggest some similarities between the effects of barbiturates and propofol in the brain.

The sedative effects of benzodiazepine agonists such as midazolam are mediated by interaction with the benzodiazepine receptor component of the GABA_A receptor complex. Receptor occupancy by a benzodiazepine agonist causes an increase in the affinity of the inhibitory neurotransmitter GABA for its receptor, leading to potentiation of GABA-mediated chloride conductance and neuronal inhibition [17, 18]. Benzodiazepines also have actions similar to, but probably less pronounced than, those described for propofol in the spinal cord and in nor-adrenergic pathways [18].

The possibility that the observed synergism was caused by alterations in drug disposition cannot be excluded as the pharmacokinetic profile of propofol has not been studied in the presence of midazolam. Such an interaction was found for propofol and fentanyl, where a 50% increase in the mean arterial concentrations of propofol in the presence of fentanyl 100 µg was observed [19]. However, a more recent, slightly larger study has failed to confirm this finding [20] and it was suggested that the findings of the original study resulted from analysing data from a small number of subjects with widely variable pharmacokinetic profiles. Another problem with suggesting the observed synergism was caused by a pharmacokinetic interaction is that such an explanation does not explain why midazolam acted as if it were an anaesthetic agent when combined with propofol.

Arterial pressure was assessed only for a short interval after induction and this may account for the lack of correlation between dose of drug and degree of hypotension. However, the similar decrease in arterial pressure observed with the combination as with equipotent sedative doses of the individual drugs indicates that synergism extended to the hypotension that occurred at induction of anaesthesia.

In summary, we have shown that the combination propofol-midazolam is synergistic when used in the commonly accepted dose range. For hypnosis, using the combination, a 44% reduction in the ED₅₀ of each agent individually was found and for anaesthesia the addition of midazolam

0.13 mg kg⁻¹ caused a 52% reduction in the dose of propofol required. The results are similar to those found for a thiopentone-midazolam combination and are consistent with postulated actions for propofol at GABA_A receptors. The combination may prove useful for sedation, induction and maintenance of anaesthesia.

ACKNOWLEDGEMENT

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REFERENCES

- Short TG, Galletly DC, Plummer JL. The hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *British Journal of Anaesthesia* 1991; 66: 13-19.
- Tverskoy M, Fleishman G, Bradley EL, Kissin I. Midazolam-thiopental anesthetic interaction in patients. *Anesthesia and Analgesia* 1988; 67: 342-345.
- Ben-Shlomo I, Abd-el-Khalim H, Ezry J, Zohar S, Tverskoy M. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *British Journal of Anaesthesia* 1990; 64: 45-47.
- Vinik HR, Bradley EL, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesthesia and Analgesia* 1989; 69: 213-217.
- Kissin I, Vinik HR, Castillo R, Bradley EL. Alfentanil potentiates midazolam-induced unconsciousness in sub-analgesic doses. *Anesthesia and Analgesia* 1990; 71: 65-69.
- Cross G, Gaylard D, Lim M. Atropine induced heart rate changes: a comparison between midazolam-fentanyl-propofol-N₂O and midazolam-fentanyl-thiopentone-enflurane-N₂O anaesthesia. *Canadian Journal of Anaesthesia* 1990; 37: 416-419.
- Schultz A, Katz R, Pavlin E. A comparison of ulnar nerve tetanic stimulation and clamping of anterior axillary fold to surgical incision for the determination of MAC. *Anesthesiology* 1987; 67: A669.
- Finney DJ. *Probit Analysis*, 2nd Edn. Cambridge: Cambridge University Press, 1962.
- Plummer JL, Short TG. Statistical modelling of the effects of drug combinations. *Journal of Pharmacological Methods* 1990; 23: 297-309.
- Dobson AJ. *An Introduction to Statistical Modelling*. London: Chapman and Hall, 1983; 74-90.
- McCullum JSC, Dundee JW, Halliday NJ, Clarke RSJ. Dose response studies with propofol ('Diprivan') in unpremedicated patients. *Postgraduate Medical Journal* 1985; 61: 85-87.
- Cummings GC, Dixon J, Kay NH, Windsor JPW, Major E, Morgan M, Sear JW, Spence AA, Stephenson DK. Dose requirements of ICI 35,868 (Propofol, 'Diprivan') in a new formulation for induction of anaesthesia. *Anaesthesia* 1984; 39: 1168-1171.
- Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam, pharmacology and uses. *Anesthesiology* 1985; 62: 310-324.
- Lodge D, Anis AA. Effects of ketamine and three other

- anaesthetics on spinal reflexes and inhibitions in the cat. *British Journal of Anaesthesia* 1984; 56: 1143-1151.
15. Mason ST, King AJ, Banks P, Angel A. Brain noradrenaline and anaesthesia: Behavioural and electrophysiological evidence. *Neuroscience* 1983; 10: 177-185.
16. Haefely W, Polc P, Pieri L, Schaffner R, Laurent J-P. Neuropharmacology of benzodiazepines: Synaptic mechanisms and neural basis of action. In: Costa E, ed. *The Benzodiazepines: From Molecular Biology to Clinical Practice*. New York: Raven Press, 1983; 21-66.
17. Richards JG, Mohler H. Benzodiazepine receptors. *Neuropharmacology* 1984; 23: 233-242.
18. Haefely W, Polc P. Physiology of GABA enhancement by benzodiazepines and barbiturates. In: Olsen RW, Venter JC, eds. *Benzodiazepine-GABA Receptors and Chloride Channels: Structure and Function Properties*. New York: Alan R. Liss, 1986; 97-133.
19. Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients: Studies using single bolus injection. *British Journal of Anaesthesia* 1987; 59: 1103-1110.
20. Gill SS, Wright EM, Reilly CS. Pharmacokinetic interaction of propofol and fentanyl: single bolus injection study. *British Journal of Anaesthesia* 1990; 65: 760-765.

INTRA-ARTERIAL THIOPENTONE IS DIRECTLY TOXIC TO VASCULAR ENDOTHELIUM

R. D. MACPHERSON, L. J. MCLEOD AND A. J. GROVE

SUMMARY

Ear artery segments removed from urethane-anaesthetized rabbits were mounted, perfused with Krebs solution, and pressurized before constriction with extraluminal noradrenaline. Vessel diameter was measured using a diode array mounted above the artery. After the degree of dilatation in response to intraluminal acetylcholine and glyceryl trinitrate was measured, vessels were perfused for 120 s with solutions of either 2.5–10% thiopentone or isotonic sodium carbonate in saline of matched pH. Administration of thiopentone solutions in all concentrations resulted in destruction of endothelial cells. The dilatation of vessels to glyceryl trinitrate and their myogenic reactivity was unaltered. Isotonic solutions of sodium carbonate (pH 10.6) had no effect on either endothelial cell function or direct vasodilatation. These data show that administration of thiopentone removes arterial endothelial cells, while vascular smooth muscle function is essentially unaltered.

KEY WORDS

Anaesthetics, intravenous: thiopentone. Arteries: endothelium. Complications: arterial endothelial damage, intra-arterial injection.

Accidental intra-arterial injection of thiopentone results frequently in compromised distal blood flow which often leads to tissue ischaemia and necrosis. Since the initial reports of this phenomenon appeared more than 50 years ago [1, 2], many theories of causation have been advanced [3–8]. Some of these authors have either suggested or assumed that vascular damage may be part of this process, but definitive functional and histological evidence has been lacking. Furthermore, there has been no assessment of the importance of intimal damage in the overall pathological picture, yet it is now known that endothelial cells play a

more important part than acting as a simple mechanical barrier, and have a pivotal role in vascular mechanics through the production and release of substances such as endothelium-derived relaxing factor (EDRF) [9], and endothelin [10]. Consequently, if damage to these structures were to occur, there may be significant effects on vessel diameter and reactivity which might contribute to the overall pathological features of thiopentone-induced ischaemia. The aim of this study was to examine the effects of thiopentone on vascular smooth muscle and endothelial cell function in the isolated rabbit ear artery.

MATERIALS AND METHODS

Vessel preparation

Approval to conduct the experiments was granted by the Animal Ethics Committee of our University. New Zealand semi-lop-eared rabbits (1.5–2.5 kg) of both sexes, and aged 6–8 months, were anaesthetized with i.v. urethane 1.7 g kg⁻¹ and given heparin 1000 u i.v. The proximal 2–3 cm segment of the central ear artery was removed, avoiding contact with the vessel during dissection. Vessels were used within 12 h of their removal, stored at 2 °C in Krebs solution of the following composition (mmol litre⁻¹): NaCl 118; KCl 4.69; NaHCO₃ 25; KH₂PO₄ 1.08; CaCl₂ 2.52; MgSO₄·7H₂O 1.05; glucose 5.55; diaminoethane tetra-acetic acid (EDTA) disodium salt 0.026.

Perfusion apparatus and techniques

The apparatus used (fig. 1) was that described by Speden [11] and Speden and Warren [12],

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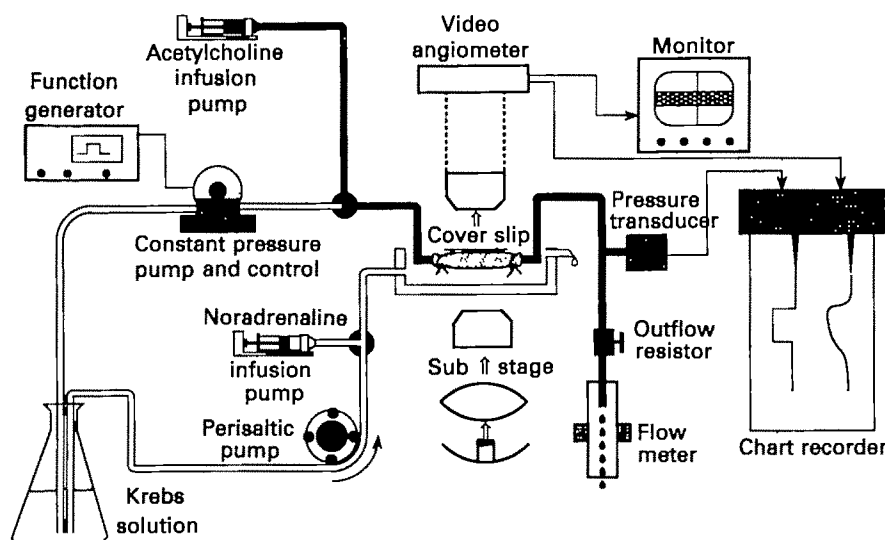


FIG. 1. Apparatus for the study of arterial reactivity. Vessels were cannulated at either end and perfused with Krebs solution while immersed in an organ bath to which noradrenaline solution was added. Glyceryl trinitrate, acetylcholine and test solutions were infused intraluminally by means of the device labelled "Acetylcholine infusion pump".

modified by the incorporation of a servo-infusion pump [13], governed by a Hewlett-Packard 3110B Function Generator, capable of maintaining constant intraluminal pressure during changes in resistance or vessel diameter. Arterial segments were transferred to a 4.2-ml prefilled organ bath, the proximal end mounted, tied onto a 19-gauge blunted cannula, and flushed out and filled with Krebs solution before the distal end was also cannulated and tied. The Krebs solution used as both the intraluminal perfusate and the organ bath exchange solution was drawn from a common reservoir, which was bubbled with 5% carbon dioxide in oxygen throughout the experiment. Intraluminal flow, which was monitored by means of a drip counter mounted distal to the outflow resistor (fig. 1), was set at 1 ml min^{-1} . The intraluminal pressure was increased to 150 mm Hg to test for leaks, and the cannulae adjusted to remove any bowing, such that the final length of the artery approximated to that *in vivo*. Any excess connective tissue was removed and the servo pump adjusted to provide a pressure of 60 mm Hg. The vessel segments, which had a final length between cannulae tips of 8–12 mm and a mean uncontracted diameter of 1.3 mm, were allowed to equilibrate under these conditions for at least 30 min. Organ bath fluid was replaced at the rate of 4 ml min^{-1} and temperature was

maintained within the limits $32\text{--}33^\circ\text{C}$ by use of circulating water, monitored by a digital thermometer (Analog Devices 2036-T-4112), using a thermocouple mounted within the bath.

The artery was illuminated from below with an Olympus LSE light source directed through a red filter and the external diameter of the vessel calculated from the width of the shadow cast by the tissue on a linear array of self-scanning photodiodes (Reticon RL1024G, U.S.A.) mounted at right angles to the long axis of the vessel. A cover slip placed across the bath well was used to remove the meniscus of the bath solution. The external diameter of the vessel was both monitored on an oscilloscope and recorded to the nearest $5 \mu\text{m}$ on a chart recorder. The intraluminal perfusion pressure was recorded using a pressure transducer (Statham, P23 Db) mounted between the artery segment and the variable outflow resistor.

Solutions of (–)-noradrenaline (Sigma) were prepared by dissolving it in hydrochloric acid $0.02 \text{ mol litre}^{-1}$ and diluting with 0.9% sodium chloride solution containing EDTA $0.026 \text{ mmol litre}^{-1}$. Using a syringe pump (Model 355, Sage Instruments USA), the noradrenaline solutions were added to the extraluminal perfusate at a rate of 0.1 ml min^{-1} to induce a constriction of the vessel of 50–60% of maximum, calculated as 0.75

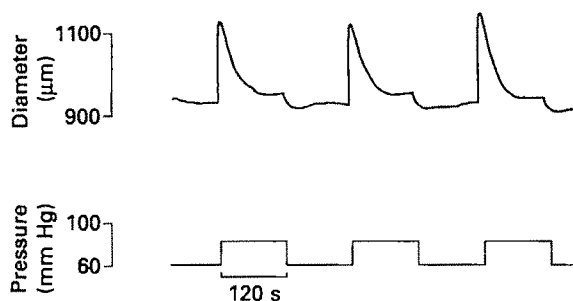


FIG. 2. Typical myogenic responses of the activated rabbit ear artery. A rapidly applied pressure increase from 60 to 80 mm Hg resulted in a prompt increase in vessel diameter. The dilatation was not maintained, however, and vessels are expected to constrict back their initial diameter against the pressure increase.

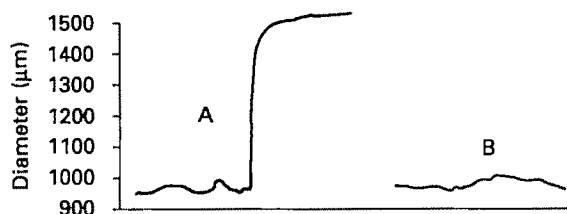


FIG. 3. Functional testing of endothelial cell integrity. Vessels with intact endothelium (A) typically demonstrate a rapid and sustained increase in diameter following infusion of acetylcholine 2×10^{-6} mol litre $^{-1}$. After endothelial removal (B), this response is not observed.

of the initial uncontracted diameter at a pressure of 60 mm Hg. The final concentration of noradrenaline in the bath was 0.350–0.475 $\mu\text{mol litre}^{-1}$.

Assessment of vascular muscle and endothelial cell function

After equilibration and activation with extraluminal noradrenaline, vessels were subjected to three separate procedures to assess their reactivity and viability. The myogenic reactivity of the vessel was assessed by its response to pressure jump increases produced using the Hewlett-Packard Waveform generator. Pressure within the vessel was increased from 60 to 80 mm Hg within 500 ms and maintained at that value for 120 s, before returning to the starting pressure. Vessels are expected to return to at least 80% of their initial diameter (D_i) despite the pressure increase (fig. 2). The presence of a functional endothelium was confirmed by a rapid and sustained dilatation following the addition of acetylcholine chloride solution (Sigma) to the intraluminal perfusate, in a final concentration of 2×10^{-6} mol litre $^{-1}$ (fig. 3A). The response of the

vessel to endothelium-independent vasodilators was determined by measurement of the degree of dilatation following the administration of glyceryl trinitrate 2×10^{-6} mol litre $^{-1}$ (DBL Laboratories).

Solutions of thiopentone were prepared by diluting ampoules of Pentothal 0.5 g (Abbott) with the accompanying diluent (Water for Injections) to produce concentrations of 2.5, 5 and 10% (w/v). Additionally, a control solution in the form of an isotonic solution of matched pH (10.6) was prepared by the addition of an appropriate amount of anhydrous sodium carbonate (Analar) to a sodium chloride solution.

After 30 min, intraluminal Krebs perfusate was ceased, and 10 ml of the selected solution of either thiopentone or sodium carbonate buffer was infused over 2 min. Care was taken not to allow air to come into contact with the vessel at any time throughout the procedure. At the conclusion of the 2-min period, a small amount of Krebs solution was flushed through the side line to remove any of the test solution remaining in the vessel and the Krebs perfusion was recommenced. The vessel was allowed to re-equilibrate for 30 min before infusions of acetylcholine and

TABLE I. Mean (SEM) vascular responses to glyceryl trinitrate 2×10^{-6} mol litre $^{-1}$ before and after infusion of either thiopentone or control solution. D_o = vessel diameter before noradrenaline activation; D_i = diameter after addition of noradrenaline; D_f = diameter after intraluminal acetylcholine

Infusion solution	D_o (μ m)	Before infusion		After infusion	
		D_i (μ m)	D_f (μ m)	D_i (μ m)	D_f (μ m)
Control ($n = 9$)	1334 (8)	881 (31)	1186 (35)	871 (38)	1169 (47)
Thiopentone					
2.5 % ($n = 7$)	1305 (7)	961 (24)	1156 (39)	893 (33)	1121 (37)
5.0 % ($n = 5$)	1327 (18)	837 (4)	1116 (84)	883 (84)	1156 (25)
10.0 % ($n = 5$)	1324 (11)	919 (53)	1213 (39)	863 (54)	1165 (35)

TABLE II. Mean (SEM) vascular responses to acetylcholine 2×10^{-6} mol litre $^{-1}$ before and after infusion of either thiopentone or control solution. D_o = vessel diameter before noradrenaline activation; D_i = diameter after addition of noradrenaline; D_f = diameter after intraluminal acetylcholine

Infusion solution	D_o (μ m)	Before infusion		After infusion	
		D_i (μ m)	D_f (μ m)	D_i (μ m)	D_f (μ m)
Control ($n = 9$)	1334 (8)	885 (48)	1227 (36)	877 (40)	1189 (33)
Thiopentone					
2.5 % ($n = 7$)	1305 (7)	953 (26)	1231 (41)	894 (45)	923 (43)
5.0 % ($n = 5$)	1327 (18)	993 (54)	1305 (15)	975 (53)	988 (54)
10.0 % ($n = 5$)	1324 (11)	909 (61)	1196 (66)	850 (48)	909 (43)

glyceryl trinitrate, and tests of myogenic reactivity detailed above were repeated. At the conclusion of each experiment, vessel segments were sent for microscope studies.

RESULTS

Arterial diameter was monitored and recorded (μ m) throughout the experimental procedures, and the following variables were calculated for each vessel:

- (1) The diameter of the vessel after mounting but before addition of noradrenaline solutions. This diameter represents maximum possible dilatation, and is referred to as the opening diameter (D_o).
- (2) The diameter of the vessel after noradrenaline activation but before addition of vasodilator test substances, referred to as the initial diameter (D_i).
- (3) The diameter following the addition of vasodilating substances, the final diameter (D_f). From these variables, a term may be derived which reflects the degree of dilatation following addition of vasodilator drugs relative to the maximum possible dilatation. This is referred to as percentage dilatation; it is calculated as $(D_f - D_i) / (D_o - D_i)$, and expressed as a percentage.

Twenty-six artery segments were removed from

11 rabbits and exposed to either control solutions of sodium carbonate ($n = 9$), or thiopentone in concentrations of 2.5 % ($n = 7$), 5.0 % ($n = 5$) or 10.0 % ($n = 5$). These segments ($n = 26$) had a mean uncontracted diameter (D_o) of 1322 (SEM 5.5) μ m. After constriction with noradrenaline, infusion of glyceryl trinitrate solution resulted in an increase in diameter of 272 (19) μ m—from 901 (18) μ m (D_i) to a mean D_f of 1167 (31) μ m. After administration of test solutions, vessels maintained their capacity to constrict to noradrenaline stimulation and there was no alteration in their response to glyceryl trinitrate (table I) irrespective of the solution used, demonstrating that, functionally, smooth muscle reactivity was unaltered. In response to acetylcholine (table II), the degree of dilatation before administration of test solutions was similar to that with glyceryl trinitrate, with a mean overall increase in diameter of 308 (20) μ m—from D_i 929 (24) μ m to D_f 1239 (21) μ m. There was no significant change in response to acetylcholine after administration of isotonic control solutions, but in vessels perfused with thiopentone in concentrations of 2.5 % or greater, the mean diameters after acetylcholine administration were significantly less (fig. 3B). These changes in diameter are presented in table

TABLE III. Percent dilatation of artery segments (mean (SEM) to acetylcholine (Ach) and glyceryl trinitrate (GTN) before and after treatment with infusion solutions

Infusion solution	Ach			GTN		
	Before (%)	After (%)	P	Before (%)	After (%)	P
Control (n = 9)	79 (5.7)	68 (7.2)	ns	70 (5.6)	68 (9.3)	ns
Thiopentone						
2.5 % (n = 7)	80 (11.8)	7.3 (1.5)	< 0.05	57 (10.8)	52 (8.0)	ns
5.0 % (n = 5)	93 (2.1)	4.1 (1.4)	< 0.05	57 (4.3)	58 (5.8)	ns
10.0 % (n = 5)	76 (13.2)	12 (2.1)	< 0.05	77 (9)	67 (5)	ns

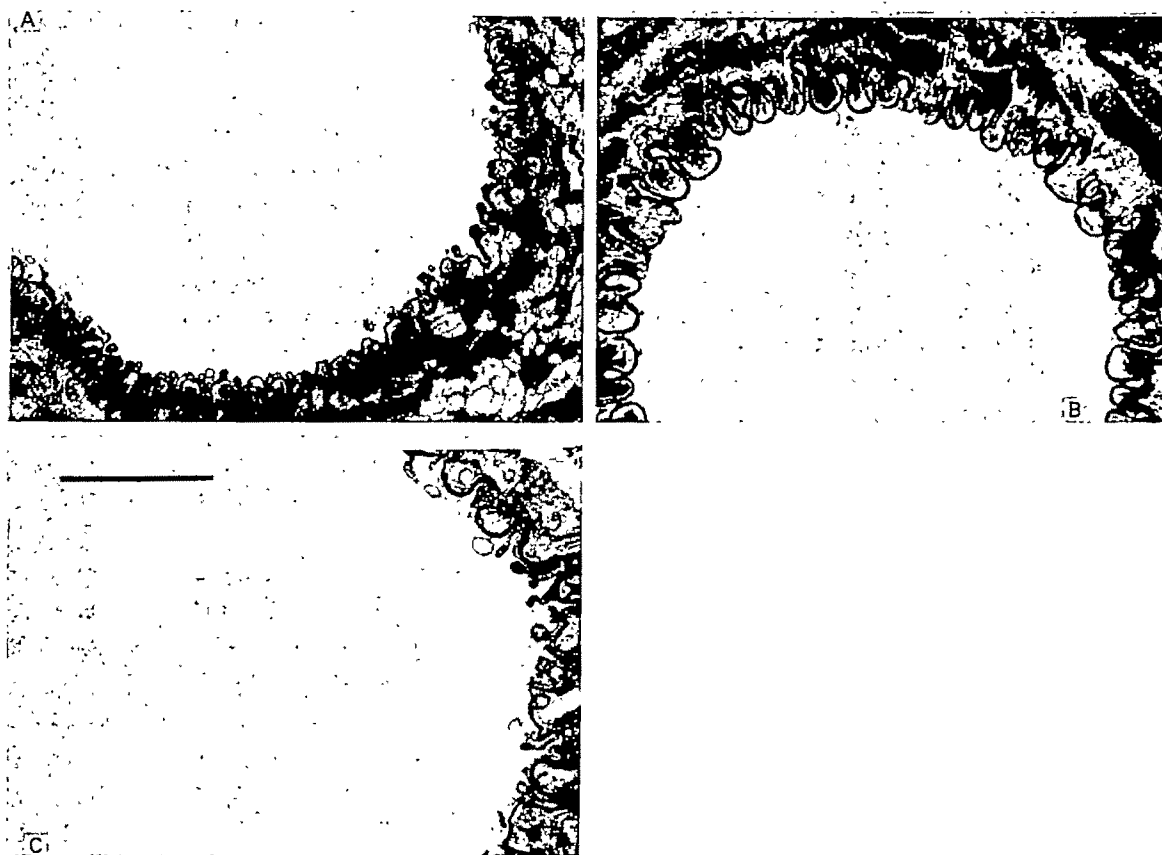


FIG. 4. Photomicrographs of rabbit ear artery sections. A: After mounting, noradrenaline activation and Krebs perfusion for 30 min, endothelial cells are clearly visible. B: After perfusion with 2.5 % thiopentone for 120 s, endothelial cells have been removed and the internal elastic lamina is exposed. C: After perfusion with control solution for 120 s, endothelial cells are undisturbed. Specimens were fixed in gluteraldehyde, postfixed in osmium tetroxide and embedded in Epon before staining with toluidine blue. Horizontal bar represents 100 μ m.

III in terms of percentage increase in dilatation. In vessels exposed to thiopentone in all concentrations, response to glyceryl trinitrate was unchanged. However, there were significant

alterations in response to acetylcholine. Percent dilatation decreased from 80 (11.8)% to 7.3 (1.5)% after infusion of the 2.5 % solution, from 93 (2.1)% to 4 (1.4)% after administration of 5 %

solution, and from 76 (13.2) % to 12 (2.1) % after administration of 10 % solution. As the dilatation response to acetylcholine is known to be dependent on release of EDRF from an intact and functional endothelium [9], these results indicate that the reactivity of these cells has been effectively destroyed by thiopentone solutions. This was confirmed anatomically by microscope studies (fig. 4). There was no difference in vascular structure after administration of control solution (fig. 4).

DISCUSSION

The pathogenesis of arterial occlusion, ischaemia and tissue necrosis seen after intra-arterial injection of thiopentone has yet to be resolved fully. Of the many theories advanced, the contemporary view held most widely seems to be that precipitation of thiopentone in the arterial tree initiates an inflammatory reaction and arteritis [8] which, coupled with the microembolization that follows [5], eventually results in occlusion of the distal circulation. These conclusions have been reached mainly using laboratory studies [4-7], confirmed to some degree by examination of vessels in limbs removed surgically [8]. Experiments studying intra-arterial thiopentone have often used the rabbit ear artery and the procedures adopted here, in terms of thiopentone concentrations and duration of administration, were designed to parallel the methods used in these earlier studies [7, 14, 15] to allow comparison of results.

Because of the complex and time-dependent pathological picture seen after intra-arterial administration of thiopentone, it is difficult to determine which of the events have been initiated by the thiopentone *per se* and which are attributable to the general inflammatory response which follows. While it would appear that it is the latter process which accounts for the eventual arteritis, these experiments have shown that concentrations of thiopentone as small as 2.5 % had direct toxic effects in that they were capable of removing vascular endothelial cells and exposing the underlying intimal layer, the process being essentially complete within 120 s. In common with the findings of others [4, 14], there was no alteration in vessel function or microstructure after administration of isotonic control solutions buffered to pH 10.6, confirming that vascular effects were secondary to thiopentone and not to the alkalinity of the injectate.

Thiopentone, even in large concentrations, had no direct effect on the smooth muscle structure and function; vascular segments remained capable of constriction to noradrenaline and dilatation to non-endothelium dependent vasodilators such as glyceryl trinitrate, and the myogenic responsiveness of the vessels was also unchanged. It is unusual that thiopentone should have such a destructive effect on endothelial cells, while leaving smooth muscle function unaffected. In laboratory procedures in which vascular endothelium is removed by chemical means, substances such as collagenase [16], saponin [17] or the detergent CHAPS [18] are used commonly, often with poor results, as they frequently either fail to remove endothelial cells, or result in damage to underlying muscle.

Earlier, it was proposed [4, 19] that arterial spasm was responsible for thiopentone-induced gangrene, a theory which has now been discarded. However, it is now known that many vessels display a basal level of flow-induced release of EDRF [20, 21], which antagonizes constrictor activity of circulating catecholamines. In this series of experiments, as in earlier studies [22], removal of the endothelium resulted in a consistent, although statistically insignificant, decrease in vessel diameter to the same concentration of extraluminal noradrenaline. Vascular preparations in which endothelial cells have been removed have been shown to be more sensitive to the effects of some inflammatory mediators and vasoconstrictor agents [23] and as it has been demonstrated that significant amounts of thromboxane are released after intra-arterial administration of thiopentone [15] and that platelet aggregation, a process which results in the production of a wide range of vasoactive substances, occurs after thiopentone and blood admixture *in vitro* [6], it is likely that there is a reduction in vessel diameter by the direct stimulation of vascular smooth muscle by inflammatory mediators.

This constriction does not constitute a "spasm", but it does lead to the conclusion, by application of Poiseuille's Law, that flow would be considerably impeded in thiopentone affected vessels where the endothelium has been removed, further compromising tissue perfusion.

It is accepted generally that the risk of initiating vascular damage with intra-arterial thiopentone increases with increasing concentration of the drug [24], and that use of the 2.5 % solution is

relatively safe [25]. Indeed, there have been only occasional case reports of gangrene after intra-arterial injection at this strength [26], with most cases being reported after the use of more concentrated solutions. Nevertheless, 2.5% solutions of thiopentone are capable of endothelial cell destruction.

In terms of treatment of the sequelae of thiopentone-induced injury, results of these experiments suggest that any strategy which utilizes endothelium-dependent vasodilatation to enhance flow in thiopentone-affected vessels is likely to be less effective than methods which are not dependent on an intact and functional endothelium.

In summary, we have shown that solutions of thiopentone of 2.5% and above acted directly to destroy vascular endothelial cells after a 120-s exposure. Vascular smooth muscle function was unaffected, and solutions of isotonic anhydrous sodium carbonate buffer of pH 10.6 had no effect. After intra-arterial administration of thiopentone, endothelial cell destruction and subsequent exposure of the intimal surface may be important processes in attenuating vessel diameter, by eliminating vascular release of EDRF and initiating or promoting thrombus formation, respectively.

REFERENCES

1. Van der Post CWH. Report of a case of mistaken injection of Pentothal sodium into an aberrant ulnar artery. *South African Medical Journal* 1942; 16: 182.
2. Macintosh RR, Heyworth PSA. Intra-arterial injection of Pentothal. *Lancet* 1943; 2: 571.
3. Cohen SM. Accidental intra-arterial injection of drugs. *Lancet* 1948; 2: 361-371.
4. Burn JH, Hobbs R. Mechanism of arterial spasm following intra-arterial injection of thiopentone. *Lancet* 1959; 1: 1112-1115.
5. Waters DJ. Intra-arterial thiopentone: A physico-chemical phenomenon. *Anaesthesia* 1966; 21: 346-356.
6. Brown SS, Lyons SM, Dundee JW. Intra-arterial barbiturates. *British Journal of Anaesthesia* 1968; 40: 13-19.
7. Ellertson DG, Lazarus HM, Auerbach R. Patterns of acute vascular injury after intra-arterial barbiturate injection. *American Journal of Surgery* 1973; 126: 813-817.
8. Stone HH, Donnelly CC. The accidental intra-arterial injection of thiopental. *Anesthesiology* 1961; 22: 995-1006.
9. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature (London)* 1980; 288: 373-376.
10. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Maki T. A novel potent vasoconstrictor peptide produced by vascular endothelial cell. *Nature (London)* 1988; 332: 411-415.
11. Speden RN. Active reactions of the rabbit ear artery to distention. *Journal of Physiology (London)* 1984; 351: 631-643.
12. Speden RN, Warren DM. The interaction between noradrenaline activation and distension activation of the rabbit ear artery. *Journal of Physiology (London)* 1986; 375: 283-302.
13. Borgstrom P, Clemenz LA, Grande P-O. A servo controlled roller pump for constant flow or constant blood perfusion under normal pulsatile or non-pulsatile conditions. *Acta Physiologica Scandinavica* 1981; 112: 437-442.
14. Kinmonth JB, Shepherd RC. Accidental injection of thiopentone into arteries. *British Medical Journal* 1959; 2: 914-918.
15. Zachary LS, Smith DJ, Heggors JP, Robson MC, Boertman JA, Niu X-T, Schileru RE, Sacks RJ. The role of thromboxane in experimental inadvertent intra-arterial drug injections. *Journal of Hand Surgery* 1987; 12A: 240-245.
16. Furchgott RF, Carvalho MH, Khan MT, Matsunaga K. Evidence for endothelial-dependent vasodilation of resistance vessels by acetylcholine. *Blood Vessels* 1987; 24: 145-149.
17. Samata K, Kimura T, Satoh S, Wantabe H. Chemical removal of the endothelium by saponin in the isolated dog femoral artery. *European Journal of Physiology* 1986; 128: 85-91.
18. Kuo L, Chillian WM, Davis MJ. The coronary arteriolar myogenic response is independent of the endothelium. *Circulation Research* 1990; 66: 860-866.
19. Burn JH. Why thiopentone injected into an artery may cause gangrene. *British Medical Journal* 1960; 2: 414-416.
20. Lampling KG, Dole WP. Flow-mediated dilatation attenuates constriction of large coronary arteries to serotonin. *American Journal of Physiology* 1988; 255: H1317-H1324.
21. Rubyani GM, Romero JC, Vanhoutte PM. Flow-induced release of endothelium-derived relaxing factor. *American Journal of Physiology* 1986; 250: H1145-H1149.
22. MacPherson RD, McLeod L, Rasiyah R. Myogenic response of isolated pressurized rabbit ear artery is independent of endothelium. *American Journal of Physiology* 1991; 260: H779-H784.
23. Vanhoutte PM, Houston DS. Platelets, endothelium, and vasospasm. *Circulation* 1985; 72: 728-734.
24. Dundee JW. *Thiopentone and Other Thiobarbiturates*. Edinburgh: Livingstone, 1956.
25. Mark LC. A lone case of gangrene following intraarterial thiopental 2.5%. *Anesthesiology* 1983; 59: 153.
26. Dohi S, Naito H. Intraarterial injection of 2.5% thiamylal does cause gangrene. *Anesthesiology* 1983; 59: 154.

JUGULAR BULB CANNULATION: DESCRIPTION OF A CANNULATION TECHNIQUE AND VALIDATION OF A NEW CONTINUOUS MONITOR

P. J. D. ANDREWS, N. M. DEARDEN AND J. D. MILLER

SUMMARY

We have compared *in vivo* oxygen saturation recordings obtained from the Oximetrix 3 with *in vitro* measurements using the Instrumentation Laboratories 282 Co-Oximeter. The small mean difference (0.85%) and close limits of agreement (-4% to 6%) are close enough for clinical purposes, provided *in vivo* calibration is performed after insertion of the fiberoptic catheter and repeated at least every 12 h. Continuous monitoring of jugular bulb oxygen saturation during intensive care of brain injured patients is now possible using fiberoptic technology. This technique may be of value in detecting global ischaemia, and as a predictor and monitor of cerebral perfusion pressure therapy.

KEY WORDS

Brain: head injury, ischaemia. Equipment: continuous *in vivo* oximetry. Monitoring: jugular bulb oxygen saturation.

The potential advantages of monitoring jugular venous oxygen saturation (Sjv_{O_2}) in intensive care management of severely head injured patients include: detection of impending global cerebral ischaemia [1], monitoring the effects of increasing intracranial pressure (ICP) on cerebral blood flow: cerebral metabolic rate ratio (CBF:CMR) [2, 3] and monitoring the effect of therapeutic interventions [4-6].

Continuous recording of Sjv_{O_2} would be superior to intermittent sampling for detection of ischaemic events and monitoring therapy for increased ICP [7]. However, currently available reflectance spectrophotometric catheters have only been evaluated and verified with transmission oximetry *in vitro*, in the pulmonary artery [8, 9] but not in the jugular bulb.

The aim of this study was to compare continuous Sjv_{O_2} recordings from the 40-cm Shaw

Opticath and Oximetrix 3 Computer, by comparison with intermittent anaerobic samples measured on the ILS Co-Oximeter 282 and to determine any drift in the continuous Sjv_{O_2} readings over 24 h.

PATIENTS AND METHODS

We studied 25 patients with severe head injury (admission, after resuscitation, Glasgow Coma Score of 8 or less) treated on the neurosurgical ICU with sedation (phenoperidine and midazolam infusions), paralysis and IPPV to mild hypocapnia (P_{aCO_2} 3.5-4 kPa).

Oximetrix 3 System

The Oximetrix 3 System (OX3) is an *in vivo* reflection spectrophotometric oximeter. The system includes a processor, optical module and a fiberoptic catheter. A pulmonary artery catheter, a 25-cm and a 40-cm catheter are available. We have studied the Shaw Opticath 40-cm catheter with this system, which uses three wavelengths of light to calculate two reflected light intensity ratios; this is superior to two-wavelength systems [9]. Light of red and near infra-red wavelengths is transmitted down the catheter at 1-ms intervals and absorbed, reflected and refracted by the adjacent red blood cells. Reflected signals from a photoelectric sensor are averaged for the previous 5 s and updated every 1 s. A Digital Signal Filter

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rejects artefact caused by the catheter tip hitting the vessel wall.

Catheter insertion

Cerebral blood drains from the intracranial venous sinuses into the sigmoid sinuses and thence into the internal jugular veins via the jugular foramina. The bulbous dilatation of the jugular vein just below the base of the skull thus contains cerebral venous blood. It is usually the biggest vein in the neck. The right jugular vein is usually larger than the left and is generally believed to drain most of the blood from the cerebral hemispheres with blood from the posterior fossa contents draining into the left vein. It descends in contact with the lateral side of the internal and common carotid arteries, enclosed with them and the vagus nerve in the carotid sheath. It ends posterior to the medial part of the clavicle by joining the subclavian vein to form the brachiocephalic vein. Numerous extracranial veins join the internal jugular vein throughout its passage in the neck: inferior petrosal sinus; pharyngeal plexus; facial vein; lingual vein; superior thyroid veins; middle thyroid vein; jugular lymph trunk. Therefore, to monitor the Sjv_{O_2} of cerebral blood correctly, the catheter tip must be placed high in the bulb.

Contraindications to this technique include bleeding diathesis, local infection, local neck trauma or any impairment to cerebral venous drainage.

In the normal brain, measurement of jugular bulb oxygen saturation is similar whether the left or right side is used [10]. In the abnormal brain it has been recommended to use the vein ipsilateral to the major pathology [2]. However, as cerebral venous drainage varies, the side of predominant cerebral venous drainage should probably be chosen for optimal Sjv_{O_2} monitoring in preference to the side of intracranial pathology. To ascertain the predominant side, patients are positioned with 10–15° of head-up tilt with the head in mid-position. The effect of temporary manual occlusion of both veins on intracranial pressure and cerebral perfusion pressure (CPP) is noted. Before occlusion, baseline recordings of the above variables are taken. Then, in turn, right and left veins are occluded with repeated readings of ICP, arterial pressure and CPP before, during and after occlusion. If the maximum change in ICP is the same, the side of the lesion (main lesion by CT scan) is used or, in diffuse injury, the right side.

Patients are then placed flat (provided ICP remains less than 20 mm Hg) with the head tipped slightly away from the side of insertion. The neck and upper thorax are prepared with antiseptic solution. The carotid artery is palpated on the appropriate side medial to sternocleidomastoid muscle at the level of the inferior border of the thyroid cartilage. Local anaesthetic is infiltrated into the skin lateral to carotid pulsation. The internal jugular vein is cannulated percutaneously by advancing a needle from this insertion point towards the external auditory meatus. After successful cannulation, a 14-French gauge Vygon LeaderCath is inserted using a Seldinger technique to act as an introducer, and flushed with heparinized saline.

The 40-cm Shaw Opticath is connected to the optical module and a pre-insertion calibration performed to test the integrity of the system. The catheter is withdrawn gently from the reference optical cuvette and the sampling port connected to the heparinized saline flush. The Opticath is now advanced into the internal jugular vein through the 14-French gauge introducer, to avoid kinking of the catheter in the neck, until the tip is felt to abut on the base of the skull or 15 cm of catheter has been inserted. The introducer is then withdrawn carefully over the Opticath, thereby avoiding displacement. The system is secured with sutures and a sterile dressing applied.

The position of the Opticath is checked radiologically to verify optimal placement of the catheter tip in the jugular bulb, above the lower border of C1, and to detect kinks in the catheter. This placement minimizes contamination from extracranial feeding vessels and reduces the risk of the catheter tip abutting against the base of the skull or the vessel wall.

Procedure

A Shaw Opticath was inserted into the internal jugular vein on the side of maximum change in ICP on jugular occlusion. The jugular occlusion test was then repeated and the catheter was left *in situ* only if the difference (before and after insertion) in maximum ICP during manual occlusion of the vein opposite to cannulation was less than 5 mm Hg.

Before insertion, the Shaw Opticath was calibrated against a reference cuvette provided with the catheter. Subsequent reflected light intensity ratios during *in vivo* monitoring were then compared with this standard. Pre-insertion cali-

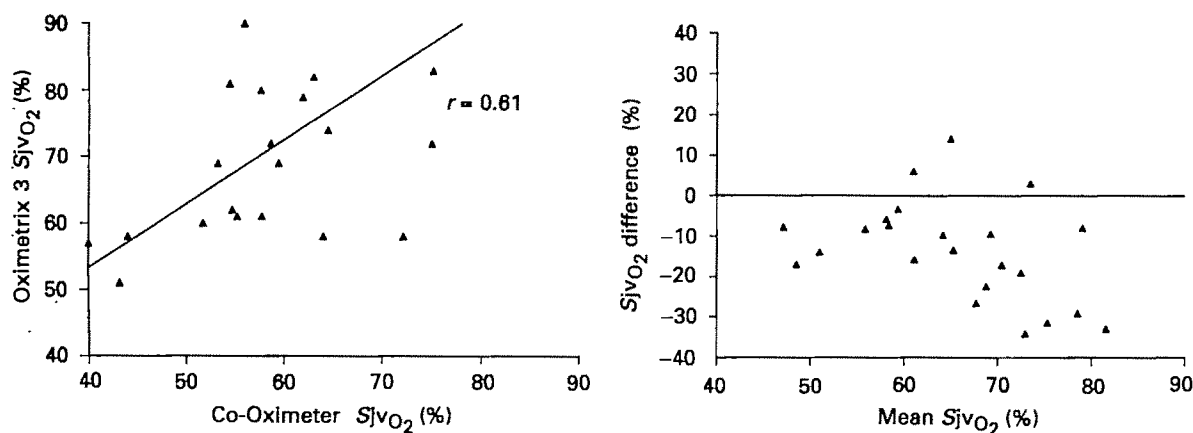


FIG. 1. Left: Plot of jugular venous oxygen saturation ($SjvO_2$) by Co-Oximeter vs Oximetry 3, showing a poor correlation with a wide scatter after pre-insertion calibration. Right: Plot of mean jugular venous oxygen saturation vs the difference between the two methods of measurement, demonstrating over-reading by the Oximetry 3.

bration acts as a check of the entire system. After correct placement of the catheter tip had been established by radiographs or an image intensifier, a light intensity calibration (monitoring of catheter position in the blood vessel, detection of obstruction of the catheter and artefact caused by vessel wall) was performed and subsequent light intensities displayed continuously. The resultant $SjvO_2$ recordings were compared with anaerobically taken samples measured on an ILS Co-Oximeter, after which an *in vivo* calibration was made matching OX3 recordings with those from an *in vitro* transmission co-oximeter. However, after *in vivo* calibration, the system must make the assumption that the oxygen saturation lies on a curve in the middle of a range of light intensity ratios and if the physiological variables (pH, temperature and PCV) change, the subsequent reflected light intensity ratio reflects a wider range of $SjvO_2$ values than is obtained using the pre-insertion standard reference. A light intensity calibration is performed automatically with *in vivo* calibrations.

The Co-Oximeter was maintained regularly and calibrated and standardized daily to known reagents.

An *in vivo* calibration was performed daily to assess drift. During the intervening 24-h period, regular samples were measured on the *in vitro* Co-Oximeter and compared with the measurements from the optical catheter. The observer analysing the anaerobic samples (*in vitro* measurement) was blind to the recordings from Oximetry 3 (*in vivo*

continuous recordings). Carboxyhaemoglobin and methaemoglobin concentrations were less than 2% during the study.

Statistics

The two methods of measurement were compared using linear regression [11] and the technique of analysis for method comparison studies described by Altman and Bland [12]. This evaluates agreement between the two methods of measurement.

RESULTS

All cannulation attempts were successful and no complications were observed. Two hundred and eleven paired recordings were taken in 25 patients using 26 catheters.

Following pre-insertion calibration, there was significant correlation ($r = 0.61$, $P < 0.001$, $n = 26$) between jugular saturation measurements by the two methods. However, the large mean difference in saturation between the two methods of measurement ($\bar{d}$, -10.8%) (Co-Oximeter - Oximetry 3; the data were normally distributed), and the wide limits of agreement ($\bar{d} \pm 1.96 \times \text{SD of } \bar{d}$) (LA, -37 to 11%) are unsatisfactory for clinical measurement. There was bias following pre-insertion calibration, the catheter over-reading (95% confidence interval of bias ($\bar{d} \pm (t \times \text{SEM } \bar{d})$) (CIB) -17.7 to -7.7%) (fig. 1).

After *in vivo* calibration, fluctuations in OX3 recordings closely correlated with the Co-Oxim-

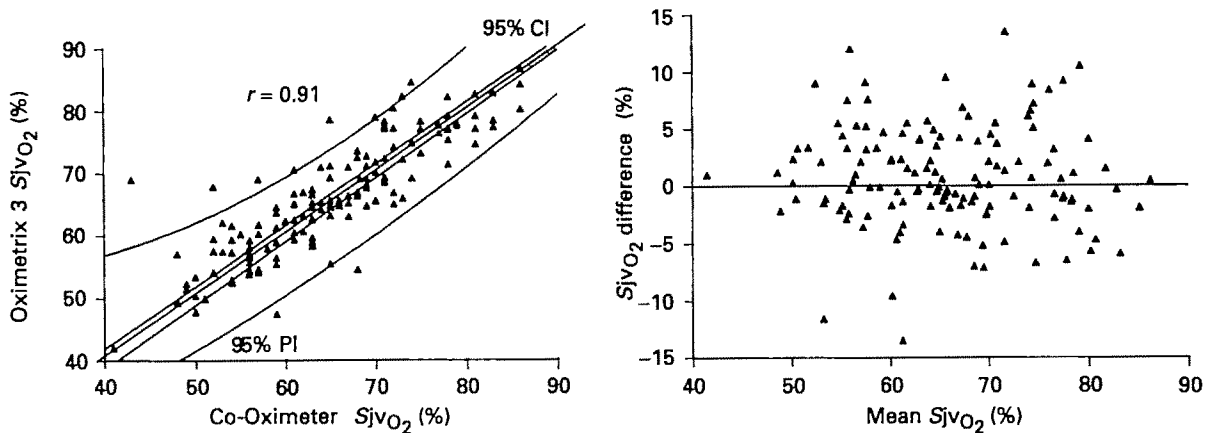


FIG. 2. Left: Plot of jugular venous oxygen saturation ($SjvO_2$) by Co-Oximeter *vs* Oximetry 3, showing a good correlation with a narrow scatter following *in vivo* calibration. Ninety-five percent confidence (CI) and prediction (PI) intervals are shown. Right: Plot of mean jugular venous oxygen saturation *vs* the difference between the two methods after *in vivo* calibration, demonstrating close limits of agreement and no bias.

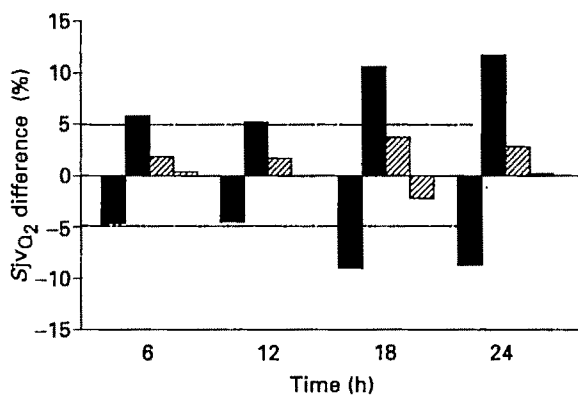


FIG. 3. Plot of the difference in jugular venous oxygen saturation ($SjvO_2$) between the two methods against time showing a deterioration in the limits of agreement (■) after 12 h. ▨ = Confidence interval of bias.

eter (fig. 2, regression line with 95% confidence and prediction interval [11]) over a period of 24 h ($r = 0.91$, $P = 0$, $n = 185$).

Paired recordings were analysed in four time epochs following *in vivo* calibration and agreement and bias calculated: 0–6 h LA -4.6 to 5.8% , CIB 0.38 to 1.8% ; 6–12 h LA -4.5 to 5.2% , CIB -0.05 to 1.7% ; 12–18 h LA -9 to 10.6% , CIB -2.2 to 3.7% ; 18–24 h LA -8.7 to 11.7% and CIB 0.2 to 2.8% (fig. 2).

During the first 12 h after *in vivo* calibration the mean difference was small, 0.85% , and the limits of agreement close enough for clinical purposes

(-4.5% to 5.2% , $n = 105$) with no bias (CIB, 0.3 to 1.7%). However, after 12 h, the mean difference remained small ($\bar{d} = 0.75\%$), but agreement between the two methods of measurement deteriorated (LA -8.7 to 11.7% , $n = 80$). No bias was noted (CIB -0.8 to 2.8%). Recalibration is therefore recommended every 12 h (fig. 3).

After *in vivo* calibration, change in PCV, hydrogen ion concentration or temperature may affect the agreement between the two systems. Two-way analysis of variance (ANOVA) of the change in temperature, PCV and hydrogen ion concentration (change over 24-h period from the value obtained at *in vivo* calibration) failed to demonstrate a significant contribution from any of these physiological factors to the difference in saturation recordings and deterioration in agreement between the recordings from these two systems.

We have now used this system to monitor $SjvO_2$ for 113 days in 25 patients. In the majority of head injury patients, $SjvO_2$ remained at 50 – 70% . Ischaemic values ($< 40\%$) of $SjvO_2$ were encountered during hyperventilation, after focal severe head injury, after evacuation of intracranial haematoma and during plateau waves. Desaturation was seen during episodes of systemic hypotension and arterial hypoxaemia and occasionally with hypnotic therapy.

Increased ICP (without plateau waves) may be associated with an increased ($> 75\%$) or normal $SjvO_2$. Our current view is that increased ICP

associated with hyperaemia responds best to hyperventilation, hypnotic therapy, or both. It is most frequent in children with diffuse head injury occurring predominantly in the first 48 h after trauma. However, our experience in adults is that increased ICP associated with hyperaemia usually reflects a secondary cause. In the majority of adult patients with increased ICP not arising from secondary causes, Sjv_{O_2} is in the normal range. In these patients, mannitol appears to be the most effective therapy. In any event, ICP reduction therapy with hypnotic agents or mannitol must produce a sustained increase in CPP. In our experience, successful ICP reducing therapy (increasing CPP) is invariably associated with recordings of increased Sjv_{O_2} .

DISCUSSION

The principal reason for poor agreement between the two methods of measurement following *in vitro* calibration may be related to blood flow around the catheter. During measurement of Sv_{O_2} in the pulmonary artery, for which the instrument was designed, blood is flowing away from the tip of the optical fibres and the blood is pulsatile. In the case of the jugular bulb, blood is flowing towards the catheter and is much less pulsatile. This creates different conditions for the reflection of light and thus the apparent difference in accuracy observed between Sv_{O_2} and Sjv_{O_2} measurement after *in vitro* calibration.

Several factors could account for the difference in saturation recordings between the two methods after *in vivo* calibration:

(1) Kinking of the catheter may produce spurious recordings without causing a light intensity alarm. Kinking can occur both within and outside the patient. When the coil is within the internal jugular vein, this can be detected only by x-ray. This occurred after 24 h in two of our patients and may have developed because the catheter was tethered at the skin and lateral rotation of the patient's head resulted in the base of the skull deflecting the catheter down the vein. Coiling may have resulted because the catheter expands and lengthens as it warms up. Kinking results in non-physiological swings in Sjv_{O_2} without a change in light intensity. If this occurs, lateral neck radiograph should be performed to exclude coiling within the internal jugular vein.

(2) After *in vivo* calibration, change in PCV, hydrogen ion concentration or temperature may

affect the agreement between the two systems. However, ANOVA of the change in temperature, PCV and hydrogen ion concentration failed to demonstrate a significant contribution to the difference in saturation recordings.

(3) The deterioration with time may be a result of fibrin or clot deposition. All catheters are flushed continuously with heparin 2 iu ml^{-1} at 3 ml h^{-1} .

Most studies to date report results from intermittent sampling. Obrist and others [14] found luxury cerebral perfusion in 55 % of head injured patients, and of those with increased intracranial pressure, 77 % had increased Sjv_{O_2} recordings and decreased arterio-jugular venous oxygen concentration difference (corrected for Pa_{CO_2}). We report a lower incidence (12 % over all) of hyperaemia, probably related to differences in management regimens and errors with intermittent sampling. In reports of head injured patients with increased ICP, hyperventilation produced ischaemia in some patients [4], as did hypnotics [5], and this is in accordance with our findings. As different treatment regimens are likely to be effective in certain subgroups of head injury [6], Sjv_{O_2} monitoring could be useful to monitor the efficacy of therapy and probably predict which treatment might be most effective, thus avoiding potentially harmful therapeutic manoeuvres.

The pre-insertion calibration of OX3 was designed for use with pulmonary artery catheters. In previous studies, correlation between pre-insertion calibration and *in vitro* measurements was reported as $r = 0.994$ [8, 9]. After pre-insertion calibration with the jugular catheter, OX3 over-reads. Thus, while pre-insertion calibration is useful as a check of the integrity of the system, *in vivo* calibration is essential before measurement of Sjv_{O_2} and must be repeated at least every 12 h.

REFERENCES

1. Robertson CS, Grossman RG, Goodman JC, Narayan RK. Predictive value of cerebral anaerobic metabolism with cerebral infarction after head injury. *Journal of Neurosurgery* 1987; 67: 361-368.
2. Robertson CS, Narayan RK, Gokaslan ZL, Pahwa R, Grossman RG, Caram P, Allen E. Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. *Journal of Neurosurgery* 1989; 70: 222-230.
3. Cruz J, Miner ME, Allen SJ. Modulating cerebral oxygen delivery in coma following diffuse brain injury. *Society of Neurosciences Abstract* 1984; 10: 542.

4. Obrist WD, Langfitt TW, Jaggi JL, Cruz J, Gennarelli TA. Cerebral blood flow and metabolism in comatose patients, with acute head injury: relationship to intracranial hypertension. *Journal of Neurosurgery* 1984; 61: 241-253.
5. Bricolo AP, Glick P. Barbiturate effects on acute experimental intracranial hypertension. *Journal of Neurosurgery* 1981; 55: 397-406.
6. Dearden NM, Miller JD. Paired comparison of hypnotic and osmotic therapy in the reduction of intracranial pressure after severe head injury. In: Hoff JT, Betz AL eds. *Intracranial Pressure VII*. Berlin, Heidelberg: Springer-Verlag, 1989.
7. Garlick R, Bihari D. The use of intermittent and continuous recordings of jugular venous bulb oxygen saturation in the unconscious patient. *Scandinavian Journal of Clinical and Laboratory Investigation* 1987; 47: 47-52.
8. Nelson LD. Continuous venous oximetry in surgical patients. *Annals of Surgery* 1986; 203: 329-333.
9. Gettinger A, De Traglia MC, Glass M. *In vivo* comparison of two mixed venous saturation catheters. *Anesthesiology* 1987; 66: 373-375.
10. Gibbs EL, Lennox WG, Gibbs FA. Bilateral internal jugular blood. Comparison of arteriovenous differences, oxygen-dextrose ratios and respiratory quotients. *American Journal of Psychiatry* 1945/46; 102: 184-190.
11. *MINITAB Reference Manual*, Release 7. State College, Pennsylvania 16801: Minitab inc., 1989; 7-10-7-11.
12. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *Statistician* 1983; 32: 307-317.
13. Obrist WD, Cruz J, Jaggi JL, Langfitt TW. Cerebral blood flow and intracranial hypertension in acute head injury. *Journal of Cerebral Blood Flow and Metabolism* 1983; (Suppl. 1): 567-568.

KETAMINE FOR CAUDAL ANALGESIA IN CHILDREN: COMPARISON WITH CAUDAL BUPIVACAINE

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SUMMARY

Fifty children undergoing inguinal herniotomy were allocated randomly to three groups to receive a caudal injection of either 0.25% bupivacaine 1 ml kg⁻¹ with or without ketamine 0.5 mg kg⁻¹ or ketamine 0.5 mg kg⁻¹ with normal saline 1 ml kg⁻¹. There was no significant difference in quality of pain relief, postoperative behaviour or analgesic requirements between the ketamine group and the two other groups. The bupivacaine-ketamine mixture provided better analgesia than the bupivacaine solution alone. Side effects such as motor weakness or urinary retention were not observed in the ketamine group.

KEY WORDS

Analgesia: paediatric, postoperative. Analgesics: ketamine. Anaesthetic techniques: caudal. Anaesthetics, local: bupivacaine.

Caudal analgesia with bupivacaine is used commonly for pain relief in children [1]. More recently, the use of caudal morphine has been extended to children and has also been demonstrated to result in good analgesia [2], but has been associated with side effects, in particular, delayed respiratory depression [2, 3].

Ketamine has analgesic properties which are mediated by different mechanisms. Analgesia after periaqueductal administration of ketamine and its antagonism by naloxone suggested an opioid mechanism of analgesia [4]. This was disputed by Tung and Yaksh, who found that analgesia was reversed by methysergide but not by naloxone, suggesting a serotonergic mechanism [5]. Further, it has been shown that ketamine and phencyclidine selectively reduced responses of

central neurones to N-methyl-aspartate [6], but this effect is not known to mediate analgesia.

Animal experiments [7] showed that intrathecal administration of ketamine preserved with benzethonium chloride was not associated with evidence of macroscopic or microscopic abnormalities in the spinal cord. Ketamine produces potent analgesia [8] without respiratory depression [9] and would therefore seem to be a suitable drug for pain relief. Extradural administration of ketamine has been studied by several investigators [10, 11] as an alternative to local analgesics and opioids, which are not ideal by virtue of their unwanted side effects [2, 3, 12, 13]. Extradural ketamine seemed to be a potent and safe method for postoperative analgesia in adults [10, 11].

This double-blind study was designed to compare the analgesic effectiveness of caudal administration of ketamine, bupivacaine or a mixture of both drugs in the treatment of pain after herniotomy in children.

PATIENTS AND METHODS

Institutional Review Board approval and informed consent from parents or guardians were obtained. We studied 50 boys, ASA physical status I, undergoing unilateral inguinal herniotomy. Patients were excluded from the study if a history of allergic reactions to local anaesthetics,

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TABLE I. Patient data and duration of surgery (median (range or SE median))

	Bupivacaine group (n = 20)	Bupivacaine-ketamine group (n = 15)	Ketamine group (n = 15)
Age (months)	36 (24-84)	42 (20-72)	36 (24-72)
Weight (kg)	14.6 (0.9)	15 (0.7)	16 (0.3)
Duration of surgery (min)	30 (4.3)	30 (5.7)	40 (2.8)

bleeding diathesis, aspirin ingestion in the preceding week, or pre-existing neurological or spinal disease were present.

No premedication was given and all operations were carried out under general anaesthesia, induced with thiopentone 5-6 mg kg⁻¹ i.v. or with inhalation of nitrous oxide and halothane in oxygen. In all patients, anaesthesia was maintained with 70% nitrous oxide and halothane in oxygen delivered via an Ayre's T-piece with spontaneous ventilation. No intraoperative sedatives or opioids were administered.

After induction of general anaesthesia, patients were allocated randomly to one of three groups. Children in group I received a caudal injection of plain 0.25% bupivacaine 1 ml kg⁻¹. Group II received an identical local anaesthetic dosage mixed with ketamine 0.5 mg kg⁻¹ and group III received caudal ketamine 0.5 mg kg⁻¹ in 0.9% sodium chloride using the same weight-related volumes. All blocks were performed by one investigator with the patient in the left lateral position, using a 23-gauge needle under sterile conditions. Ketamine with benzethonium chloride as the preservative was used. A small Elastoplast dressing was placed over the site of sacral hiatus in all patients.

After administration of the caudal block, heart rate and pulse oximetry were monitored continuously and arterial pressure was monitored every 5 min by an electronic oscillotonometer.

After operation the duration of surgery was noted and the patient was transferred to the recovery room. All patients were observed for 2 h in the recovery room before returning to the ward. When the child was awake, objective pain assessments, ventilatory frequency, arterial pressure and heart rate were recorded by one investigator unaware of the treatment given. Assessments were made at 15-min intervals for the first 1 h, 30-min intervals for the next 1 h and 3, 4, 6 and 24 h after recovery from anaesthesia. The observer scored pain on each occasion with reference to a three-point scale (none/insignificant pain; moderate

pain; severe pain) and demeanour was scored similarly (cheerful and calm; restless; tense or tearful). Side effects were recorded by the observer in addition to the time at which analgesia, if any, was first received (recovery-analgesia time), and the total number of analgesic doses required in the first 24 h after operation. The patient's ability to stand unaided was assessed 6 h after operation.

Postoperative analgesia (paracetamol suppository 125 mg) was prescribed for each patient and was given as required at the discretion of the nursing staff, who were unaware of the group allocation of the patients.

Further assessment 24 h after operation was made by nurses and mothers. They were asked to assess the child's behaviour at bed time on the day of operation and on the following morning, with respect to pain and quality of overnight sleep.

Data processing

All statistical analyses were carried out using BMDP (1990) statistical package (University of California Press). Kruskal-Wallis test with multiple comparisons was used for comparisons between the groups. In multiple comparisons the null hypothesis was rejected if *Z* stat is larger than the critical value *ZC*:

$$1 - \phi(ZC) = \alpha[K(K-1)]$$

where ϕ = cumulative standard normal distribution function, α = desired overall significance level, and *K* = number of groups compared.

The times at which analgesia was given were treated as being analogous to survival data. "Survival" curves were plotted to indicate the proportion of patients in each group who had received no analgesia by a given time after operation. The times at which analgesia was first received for the three groups were compared using four non-parametric linear rank tests: The Mantel-Cox (log-rank), Tarone-Ware, Breslow, and Peto-Prentice statistics. These tests compare the observed rate at which patients needed

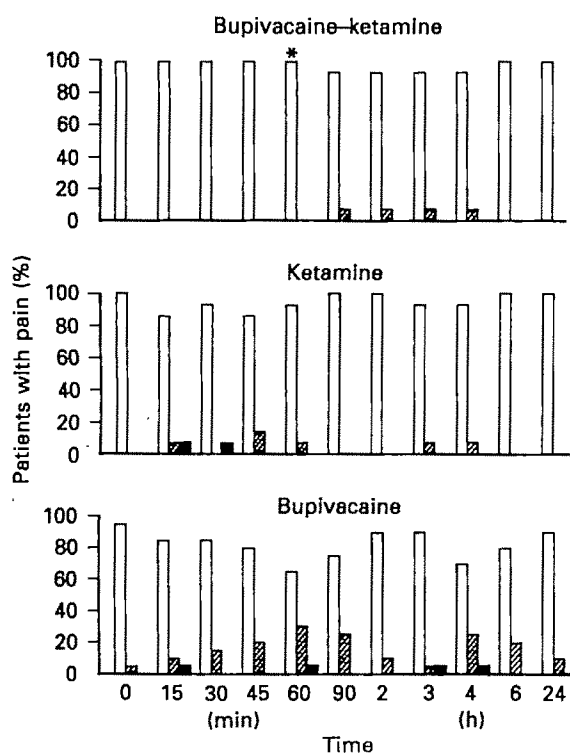


FIG. 1. Incidence of postoperative pain in the first 24 h after recovery from anaesthesia. □ = None/insignificant pain; ▨ = moderate pain; ■ = severe pain. * $P < 0.05$ vs caudal bupivacaine group.

analgesia with the rate which might be expected if caudal administration of bupivacaine, bupivacaine-ketamine and ketamine were equally effective. $P < 0.05$ was regarded as statistically significant.

RESULTS

The groups were comparable in age, weight and duration of their operations (table I).

The quality of analgesia in the group which had received a caudal injection of ketamine did not

differ from the two other groups (fig. 1). Caudal administration of bupivacaine with the addition of ketamine resulted in superior analgesia compared with caudal injection of bupivacaine alone. Significantly fewer patients in the latter group had no or insignificant pain at 60 min after recovery from anaesthesia (fig. 1). In addition, the bupivacaine group received significantly more doses of paracetamol than the bupivacaine-ketamine group in order to maintain analgesia in the first 24 h after recovery from anaesthesia (table II).

The times at which analgesia was first given are displayed in the form of survival curves in figure 2. The curves indicate the proportion of patients who received no analgesia by a given elapsed time after recovery from anaesthesia. Recovery-analgesia times were significantly longer in the bupivacaine-ketamine group than in the bupivacaine group.

There was no significant difference between the caudal ketamine group compared with the two other groups in time to first analgesia and the number of analgesic doses required in the first 24 h.

Administration of ketamine caudally either alone or in combination with bupivacaine was not associated with changes in postoperative behaviour. Significantly more patients who had received caudal ketamine either alone or with bupivacaine were described as cheerful and calm 60 and 90 min after recovery from anaesthesia (fig. 3) compared with those in the bupivacaine group.

The results from mothers' and nurses' assessments 24 h after operation showed no significant difference between the three groups with respect to pain and quality of overnight sleep. Vomiting occurred after operation in five (25%), four (27%) and two (13%) patients in the caudal bupivacaine, bupivacaine-ketamine and ketamine groups, respectively (ns).

Postoperative urinary retention was noted in two patients in the bupivacaine (10%) and

TABLE II. Requirement for analgesia during the first 24 h after operation. Number (%) of patients receiving 0-3 doses of paracetamol suppository 125 mg. * $P < 0.05$ vs caudal bupivacaine group

Analgesia (No. of doses)	Patients receiving analgesia		
	Bupivacaine group ($n = 20$)	Bupivacaine-ketamine* group ($n = 15$)	Ketamine group ($n = 15$)
0	10 (50)	14 (93)	12 (80)
1	6 (30)	1 (7)	3 (20)
2	3 (15)	0	0
3	1 (5)	0	0

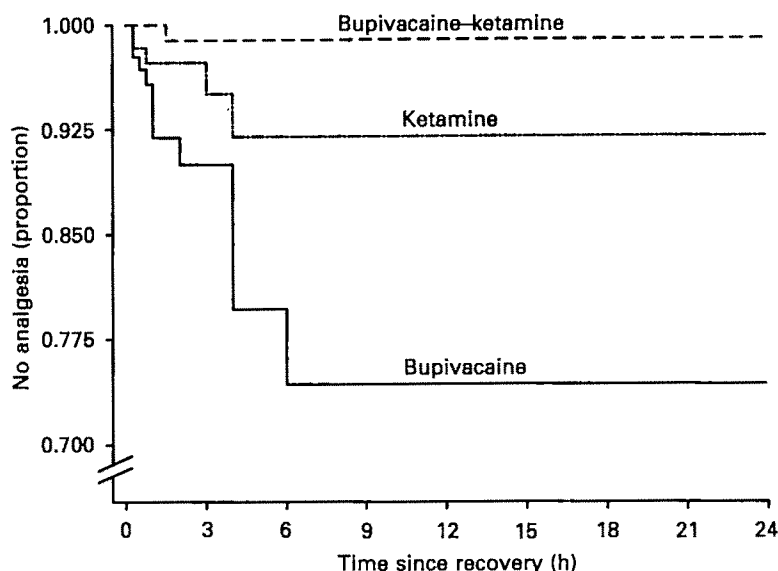


FIG. 2. "Survival" curves for the bupivacaine, bupivacaine-ketamine and ketamine groups. Proportion of patients in each group who had not required any analgesia since recovery from anaesthesia.

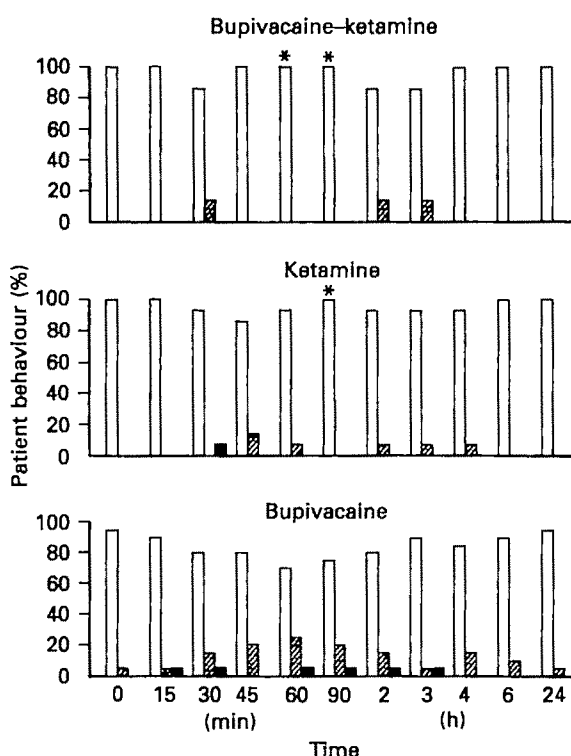


FIG. 3. Behaviour in the first 24 h after recovery from anaesthesia. □ = Calm and cheerful; ▨ = restless; ■ = tense or tearful. * $P < 0.05$ vs caudal bupivacaine group.

bupivacaine-ketamine (13%) groups, 6 h after recovery from anaesthesia. Two patients (10%) in the caudal bupivacaine group and one patient (7%) in the caudal bupivacaine-ketamine group were unable to stand 6 h after operation. In contrast, no patient in the caudal ketamine group had urinary retention or any sign of motor weakness.

No child in the first 24 h after operation had a recorded ventilatory frequency less than 12 b.p.m. or showed any significant changes in heart rate and arterial pressure. There were no instances of hypotension, bradycardia, residual paralysis or toxic reactions to bupivacaine or ketamine during or after administration of the caudal blocks.

DISCUSSION

There is considerable evidence implicating ketamine in the spinal inhibition of nociceptive transmission [4, 5, 14]. The results of the present study confirm previous reports that extradural administration of ketamine exerts modulatory influences on postoperative pain mechanisms [10, 11]. In this study, caudal administration of ketamine 0.5 mg kg^{-1} produced postoperative analgesia comparable to that associated with caudal 0.25% bupivacaine 1 ml kg^{-1} with or without ketamine.

It was noted in adults that a lesser dose of extradural ketamine (4–8 mg) did not produce significant analgesic effects [15, 16]. This observation was reported earlier by Naguib and colleagues [11], who found that ketamine 10 mg in saline 10 ml administered extradurally was ineffective in producing analgesia and all of the patients in that group required additional doses. In contrast, by increasing the dose of ketamine to 30 mg, 54% of the patients had adequate analgesia for 24 h after a single extradural injection [11].

Caudal block with bupivacaine alone can provide adequate analgesia in the early postoperative period, but as the block wears off, systemic analgesia is often required [17]. In the present study, 20% and 50% of patients in the caudal ketamine and bupivacaine groups, respectively, required additional analgesia during the first 24 h after surgery (table II). These results are similar to those of a previous report on herniotomy [18], in which 55% of patients who had caudal block with 0.25% bupivacaine 1 ml kg⁻¹ required further analgesia.

The addition of ketamine 0.5 mg kg⁻¹ to bupivacaine improved significantly both quality and duration of analgesia compared with administration of bupivacaine solution alone, without an increase in the incidence of side effects. There was a significant reduction in the amount of postoperative analgesia required by the children in the bupivacaine–ketamine group compared with those receiving bupivacaine alone. In addition, the recovery–analgesia times were significantly shorter in the latter group (fig. 2).

The overall incidence of side effects observed in the bupivacaine and bupivacaine–ketamine groups was comparable to that reported previously in children who received caudal bupivacaine [18, 19].

Respiratory depression, urinary retention and pruritis have been described in children after caudal administration of opioids [2, 3, 17], but these side effects were not encountered in this study after caudal injection of ketamine 0.5 mg kg⁻¹. Caudal ketamine was not associated with motor block, and rapid mobilization was possible in that group.

We conclude that caudal administration of ketamine 0.5 mg kg⁻¹ in children produced satisfactory postoperative analgesia after inguinal herniotomy without respiratory depression or other side effects. The quality of analgesia did not

differ significantly from that associated with caudal injection of 0.25% bupivacaine 1 ml kg⁻¹ with or without ketamine.

REFERENCES

1. Arthur DS, McNicol LR. Local anaesthetic techniques in paediatric surgery. *British Journal of Anaesthesia* 1986; 58: 760–778.
2. Krane EJ, Tyler DC, Jacobsen LE. The dose response of caudal morphine in children. *Anesthesiology* 1989; 71: 48–52.
3. Krane EJ. Delayed respiratory depression in a child after caudal epidural morphine. *Anesthesia and Analgesia* 1988; 67: 79–82.
4. Havdala HS, Borison RL, Diamond BI. Ketamine anaesthesia and analgesia: neurochemical differentiation. *Anesthesiology* 1980; 53: S57.
5. Tung AS, Yaksh TL. Analgesic effect of intrathecal ketamine in the rat. *Regional Anesthesia* 1981; 6: 91–94.
6. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *British Journal of Pharmacology* 1983; 79: 565–575.
7. Brock-Utne JG, Kallichurum S, Mankowitz E, Maharaj RJ, Downing JW. Intrathecal ketamine with preservative–histological effects on spinal nerve root of baboons. *South African Medical Journal* 1981; 61: 440–441.
8. Sadove MS, Shulman M, Hatano S, Fevold N. Analgesic effects of ketamine administered in subdissociative doses. *Anesthesia and Analgesia* 1971; 50: 452–457.
9. Soliman MG, Brinale GF, Kuster G. Response to hypercapnia under ketamine analgesia. *Canadian Anaesthetists Society Journal* 1975; 22: 486–494.
10. Islas JA, Astorga J, Loreda M. Epidural ketamine for control of postoperative pain. *Anesthesia and Analgesia* 1985; 64: 1161–1162.
11. Naguib M, Adu-Gyamfi Y, Absood GM, Farag H, Gyasi HK. Epidural ketamine for postoperative analgesia. *Canadian Anaesthetists Society Journal* 1986; 33: 16–21.
12. Martin LVH. Postoperative analgesia after circumcision in children. *British Journal of Anaesthesia* 1982; 54: 1263–1266.
13. Bromage P. *Epidural Analgesia*. Philadelphia: Saunders, 1978; 272.
14. Collins JG. Effects of ketamine on low intensity tactile sensory input are not dependent upon a spinal site of action. *Anesthesia and Analgesia* 1986; 65: 1123–1129.
15. Ravat F, Dorne R, Baechile JP, Beaulaton A, Lenoir B, Leraj P, Palmier B. Epidural ketamine or morphine for postoperative analgesia. *Anesthesiology* 1987; 66: 819–822.
16. Kawana Y, Sato H, Shimada H, Fujita N, Ueda Y, Hayashi A, Araki Y. Epidural ketamine for postoperative pain relief after gynecologic operations: a double-blind study and comparison with epidural morphine. *Anesthesia and Analgesia* 1987; 66: 735–738.
17. Wolf AR, Hughes D, Wade A, Mather A, Mather SJ, Prys-Roberts C. Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture. *British Journal of Anaesthesia* 1990; 64: 430–435.

18. Fell D, Derrington MC, Taylor E, Wandless JC. Paediatric postoperative analgesia. A comparison between caudal block and wound infiltration of local anaesthetic. *Anaesthesia* 1988; **43**: 107-110.
19. Wolf AR, Valley RD, Fear DW, Roy WL, Lerman J. Bupivacaine for caudal analgesia in infants and children: the optimal effective concentration. *Anesthesiology* 1988; **69**: 102-106.

MATERNAL TEMPERATURE REGULATION DURING EXTRADURAL ANALGESIA FOR LABOUR

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AND S. DATTA

SUMMARY

We have studied the effect of analgesia on maternal temperature (oral and tympanic membrane) progression in 53 women during normal spontaneous labour. Three groups were studied: two received extradural analgesia with a continuous infusion of 0.25% bupivacaine with or without the addition of fentanyl; the third group received only parenteral opioid analgesia. All patients were afebrile and without clinical evidence of infection at the beginning of the study. Both groups of patients receiving extradural analgesia had a consistent and significant increase in temperature after approximately 5 h of analgesia; no such trend was observed in the parenteral opioid group. Alterations in mechanisms of heat dissipation may explain these findings.

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural. Analgesics: opioid. Temperature: maternal.

Infection is a common cause of maternal and neonatal morbidity during labour [1]. Thus close monitoring of maternal temperature is performed routinely in most obstetric units. However, several factors may affect the accuracy of temperature measurement during labour. Hyperventilation, sucking ice, and oxygen administration may affect oral temperature [2]. Similarly, increased lower extremity blood flow caused by extradural analgesia-induced sympathetic block may render rectal, vaginal or bladder temperature unreliable [3, 4]. Excessive perspiration during arduous labour may alter axillary temperature. Whilst tympanic membrane (TM) temperature reflects core temperature reliably [5, 6], only recently

have simple, non-invasive devices become available for routine, clinical measurement of TM temperature.

An additional factor which may complicate interpretation of maternal temperature during labour is the type of analgesia used. Fusi and colleagues reported a significant increase in temperature (oral and vaginal) when extradural analgesia was used during labour [7]. This temperature increase was seen even in the absence of signs of maternal infection. They postulated that extradurally induced sympathectomy may inhibit heat dissipation, thus resulting in an increase in temperature as labour progressed. In contrast, other investigators have noted that extradural analgesia may be associated with hypothermia, resulting from redistribution of heat from the core to the periphery, and thus heat loss to the environment [8]. Recent evidence suggests that extradural opioids may also affect thermoregulation during anaesthesia [9, 10].

The present study was conducted to investigate further the changes in oral and TM temperature during normal labour, with and without extradural analgesia. In addition, we sought to determine the effect of the addition of an opioid (fentanyl) to the extradural analgesia.

PATIENTS AND METHODS

We investigated prospectively 53 women in active labour who fulfilled the following criteria: spontaneous onset of labour at term gestation (37-41

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TABLE I. Maternal patient characteristics (mean (range or SD)).
* $P < 0.005$ (BF vs opioid, ANOVA); all other characteristics show no significant differences between groups

	Parenteral opioid ($n = 13$)	Extradural-B ($n = 20$)	Extradural-BF ($n = 20$)
Age (yr)	28 (18–38)	29 (17–41)	27 (18–41)
Height (cm)	168 (3)	168 (5)	168 (3)
Weight (kg)	74 (9)	74 (6)	74 (6)
Parity			
Primiparous	11	16	15
Multiparous	2	4	5
Rupture of membranes to delivery (h)	9.6 (3.6)	9.5 (3.9)	12.2 (6.9)
Duration second stage (min)	60 (32)	90 (42)	115 (49)*

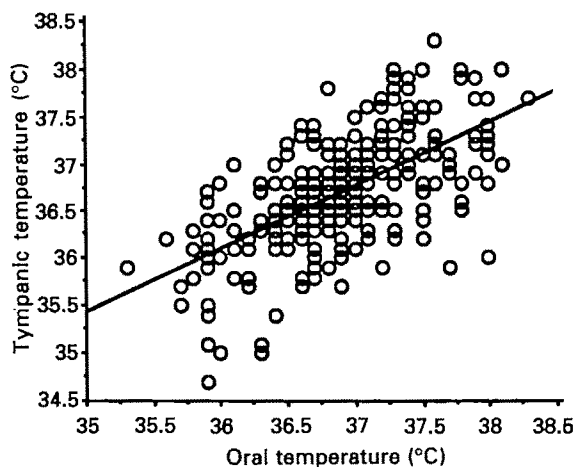


FIG. 1. Relation between oral and tympanic membrane temperatures during labour. $r = 0.62$, $P < 0.001$ (simple linear regression and ANOVA); 320 measurements shown.

weeks), intact fetal membranes or membranes not ruptured for more than 6 h, no clinical evidence or suspicion of infection, oral temperature $< 37.5^{\circ}\text{C}$, and no concurrent complications or morbidity related to pregnancy. All women gave written informed consent to the study, which was approved by the institutional review board for human subject research at Brigham and Women's Hospital.

Analgesia during labour was produced by either one or more i.v. injections of nalbuphine 10–20 mg, or extradural block. The choice of analgesia was made by the women without regard to the study. Women who requested extradural block were allocated to two groups in a randomized

fashion, using sequentially numbered, sealed opaque envelopes. Both had extradural blocks initiated with 0.25 % bupivacaine 8–12 ml. Thereafter, one group (extradural-B, $n = 20$) had a continuous extradural infusion of 0.25 % bupivacaine and the other (extradural-BF, $n = 20$) had continuous infusion of 0.25 % bupivacaine with fentanyl citrate, $2\text{ }\mu\text{g ml}^{-1}$. The infusions in both groups were maintained at 10 ml h^{-1} with a volumetric infusion pump. All extradural infusions were prepared by an anaesthetist not involved in the study, and the investigators were not aware of the patient's group assignment. Thirteen women who received only opioid analgesia served as a control group. All extradural anaesthetics were begun when cervical dilatation was between 3 and 5 cm. All women received i.v. infusions of lactated Ringer's solution at room temperature and continuous electronic fetal heart rate monitoring was used during labour.

Maternal temperature was measured using an oral sublingual thermometer (IVAC Corporation Model No. 2085, San Diego, CA, U.S.A.) and a tympanic membrane temperature sensor (Ototemp 3000, Infrared Tympanic Temperature Sensor, Exergen Corporation, Newton, MA, U.S.A.). All temperature measurements were performed in accordance with the manufacturers' instructions. The initial temperature measurement in the extradural groups was recorded immediately before performance of the block; in the parenteral opioid group the temperature measurements were begun when the patient reached 3 cm cervical dilatation and was experiencing regular, painful uterine contractions. Temperature readings (both oral and TM) were recorded hourly during labour in all patients and continued until delivery.

All labour rooms at Brigham and Women's Hospital are located below ground without windows or direct exposure to the external environment. A partially recirculating ventilation and air-conditioning system supplies approximately eight fresh air exchanges and 30 total air exchanges per hour. Ambient room temperature is maintained at $20\text{--}22^{\circ}\text{C}$.

The characteristics of the three groups were analysed with one-way analysis of variance or the chi-square test for continuous data or categorical data, respectively. The temperature measurements were compared with two-way analysis of variance with a repeated measures design. $P < 0.05$ was considered to be statistically significant.

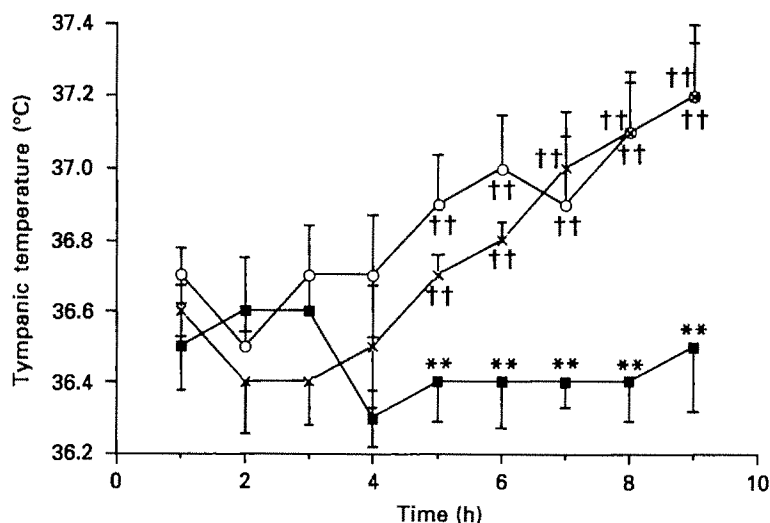


FIG. 2. Mean (SE) tympanic temperatures during labour in the extradural-BF (○), extradural-B (X) and opioid (■) groups. $P < 0.01$: **compared with extradural-BF and extradural-B groups; ††compared with pre-extradural temperature (ANOVA).

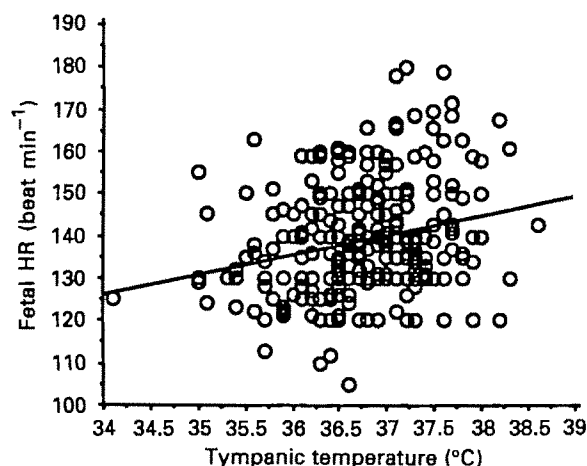


FIG. 3. Relation between tympanic temperature and fetal heart rate (HR) during labour. $r = 0.22$, $P < 0.005$ (simple linear regression and ANOVA); 320 measurements shown.

cant. Statistical analyses were performed using the Stat View II statistical package (Abacus Concepts, Inc., Berkeley, CA, U.S.A. 1987) on a MacIntosh II computer.

RESULTS

The patient characteristics of the three groups were similar (table I). There was a significant correlation between oral and TM temperature measurements ($r = 0.62$, $P < 0.001$, simple linear

regression and ANOVA) (fig. 1). The mean maternal temperatures did not differ between groups for the first 4 h of measurements. At 5 h and thereafter, the mean TM temperatures were significantly greater in both extradural groups compared with the parenteral opioid group (fig. 2). Moreover, at 5 h and thereafter, the mean TM temperatures within the extradural groups were significantly greater than the pre-extradural temperature (fig. 2). There was no evidence of temperature increase with time in the parenteral opioid group (fig. 2). There was a weak, albeit significant, correlation between fetal heart rate and maternal temperature ($r = 0.22$, $P < 0.005$) (fig. 3). No patient had signs of overt sepsis, infection or chorioamnionitis. Cultures (blood, urine or amniotic fluid) from the patients who became pyrexial showed no evidence of bacterial infection. The frequency of vaginal examinations or incidence of internal fetal monitoring did not differ among the groups.

DISCUSSION

We found a small but consistent trend toward temperature increase during labour in parturients receiving extradural analgesia compared with those receiving only parenteral opioid analgesia. The increase in temperature occurred in the absence of any clinical or bacteriological evidence of infection. These findings confirm, in essence,

the results of Fusi and colleagues [7], although the studies differ in several respects. We measured TM temperature rather than vaginal temperature, which may be affected by anaesthetic-induced sympathetic block and lower extremity vasodilatation. The temperature increased earlier in the former study, which may be attributed also to the effects of extradural block on vaginal temperature.

Marx and Loew noted a small increase in TM temperature during labour, which they attributed to uterine and skeletal muscle metabolic expenditure [11]. However, only 11 patients were studied, and the types of analgesia varied. Recent work by Kapusta and colleagues investigated skin and rectal temperatures during extradural analgesia in labour. Leg and chest temperatures increased, while core temperature did not, after extradural analgesia began [3]. This study examined temperatures for only 60 min after commencing analgesia, and the temperature trends were highly variable.

Shivering occurs commonly during labour, particularly with extradural analgesia [12]. The aetiology is multifactorial and may include a reaction to release of fetoplacental material into the maternal circulation and heat loss from the placental circulation [13, 14]. Extradural administration of opioids has been found to lessen the intensity of shivering. Altered thermoregulatory transmission from the periphery to the hypothalamus has been postulated as a possible mode for this phenomenon during extradural analgesia, although results implicating specific spinal pathways are lacking [15]. In our study, shivering occurred rarely, and we found no evidence that the extradural opioid affected the progress of temperature measurements during labour.

The clinical significance of these findings remains unclear. Although statistically significant differences between extradural and non-extradural groups were noted in the mean temperature readings during labour, this difference did not exceed 1 °C. The extradural patients, despite greater temperatures, were not clinically febrile, and there was only a weak correlation between maternal temperature and fetal heart rate. Thus it

is unlikely that this degree of temperature increase was sufficient to result in an adverse intrauterine environment with subsequent fetal compromise [16].

REFERENCES

- Schwarz RH. Amnionitis. In: Queenan JT, Hobbins JC, eds. *Protocols for High-Risk Pregnancies*. Oradell, New Jersey: Medical Economics Books, 1987; 322-326.
- Goodlin RC, Chapin JW. Determinants of maternal temperature during labor. *American Journal of Obstetrics and Gynecology* 1982; 143: 97-103.
- Kapusta L, Confino E, Ismajovich B, Rosenblum Y, David MP. The effect of epidural analgesia on maternal thermoregulation in labor. *International Journal of Gynaecology and Obstetrics* 1984; 23: 185-189.
- Imrie MN, Hall GM. Body temperature and anaesthesia. *British Journal of Anaesthesia* 1990; 64: 346-354.
- Benzinger M. Tympanic thermometry in surgery and anaesthesia. *Journal of the American Medical Association* 1969; 209: 1207-1211.
- Cork RC, Vaughn RW, Humphrey LS. Precision and accuracy of intraoperative temperature monitoring. *Anesthesia and Analgesia* 1983; 62: 211-214.
- Fusi L, Maresh MJA, Steer PJ, Beard RW. Maternal pyrexia associated with the use of epidural analgesia in labour. *Lancet* 1989; 1: 1250-1252.
- Holdcroft A, Hall GW, Cooper G. Redistribution of body heat during anaesthesia. *Anaesthesia* 1979; 34: 758-764.
- Pauca R, Savage RT, Simpson S, Roy RC. Effect of pethidine, fentanyl and morphine on post-operative shivering in man. *Acta Anaesthesiologica Scandinavica* 1984; 28: 128-143.
- Mathews NC, Corser C. Epidural fentanyl for shivering in obstetrics. *Anaesthesia* 1988; 43: 783-785.
- Marx GF, Loew DA. Tympanic temperature during labour and parturition. *British Journal of Anaesthesia* 1975; 47: 600-602.
- Workhoven MN. Intravenous fluid temperature, shivering, and the parturient. *Anesthesia and Analgesia* 1986; 65: 496-498.
- Goodlin RC, O'Connell LP, Gurth RE. Childbirth chills: Are they an immunological reaction? *Lancet* 1967; 2: 79-80.
- Clapp JF, Abrams RM. The post-partum chill. *Israeli Journal of Medical Sciences* 1976; 12: 1131-1133.
- Sevarino PB, Johnson MD, Lema MJ, Datta S, Ostheimer GW, Naulty JS. Effect of epidural sufentanil on shivering and body temperature in the parturient. *Anesthesia and Analgesia* 1989; 68: 530-533.
- Morishima HO, Glaser B, Niemann WH, James LS. Increased uterine activity and fetal deterioration during maternal hyperthermia. *American Journal of Obstetrics and Gynecology* 1975; 121: 531-538.

CLEARANCE OF ATRACURIUM AND LAUDANOSINE IN THE URINE AND BY CONTINUOUS VENOVENOUS HAEMOFILTRATION†

E. S. SHEARER, E. P. O'SULLIVAN AND J. M. HUNTER

SUMMARY

We have measured the steady state urinary clearances of atracurium, given by constant infusion, and laudanosine in eight patients undergoing artificial ventilation; all had normal renal function (mean creatinine clearance 81 ml min^{-1}). Mean (SD) urinary clearance of atracurium was $0.55 (0.5) \text{ ml kg}^{-1} \text{ min}^{-1}$; that of laudanosine was $0.33 (0.2) \text{ ml kg}^{-1} \text{ min}^{-1}$. Simultaneous plasma clearances were $7.1 (1.4) \text{ ml kg}^{-1} \text{ min}^{-1}$ and $3.8 (1.5) \text{ ml kg}^{-1} \text{ min}^{-1}$, respectively. Notional haemofiltration clearances of the two substances were measured also in seven critically ill patients with renal and respiratory failure undergoing continuous venovenous haemofiltration. Mean (SD) clearances of atracurium and laudanosine in the haemofiltrate fluid were $0.11 (0.06) \text{ ml kg}^{-1} \text{ min}^{-1}$ and $0.09 (0.02) \text{ ml kg}^{-1} \text{ min}^{-1}$, respectively whilst plasma clearances were atracurium $6.7 (1.8) \text{ ml kg}^{-1} \text{ min}^{-1}$ and laudanosine $4.5 (1.8) \text{ ml kg}^{-1} \text{ min}^{-1}$. There were no significant differences between the plasma clearances of the drugs in the two groups, despite the difference in severity of sickness. Urinary clearance rates of atracurium and laudanosine were approximately 8 and 9% of that in the plasma, but the haemofiltration clearance of both substances was only 2%.

KEY WORDS

Intensive care: haemofiltration. Kidney: urinary clearance, laudanosine. Neuromuscular relaxants: atracurium.

Although it was thought originally that atracurium was eliminated solely in the plasma and extracellular fluid by means of Hofmann degradation and ester hydrolysis, Fisher and his colleagues in 1986 [1] offered evidence from *in vivo* and *in vitro* work suggesting that organ elimination is responsible for the clearance of at least 60% of a

dose of atracurium. Measuring organ clearance of atracurium through the kidney during anaesthesia is relevant to this problem, but is impracticable: a good urine output is difficult to establish, especially during the first 1 h of anaesthesia [2] and it necessitates catheterization of the bladder, which may not be clinically indicated; in addition, steady state plasma concentrations of atracurium, which are necessary if true urinary clearance is to be measured, may not be obtained unless an infusion of the drug is used. It was decided, therefore, to study the urinary clearance of atracurium and its metabolite, laudanosine, in intensive care patients (with normal renal function) who were receiving atracurium by constant infusion during intermittent positive pressure ventilation (IPPV).

Continuous venovenous haemofiltration (CVVH), used in the treatment of patients with acute renal failure [3], is known to contribute to the elimination from the circulation of many drugs used in intensive care [4]. It was decided also to investigate the plasma and haemofiltration clearances of atracurium and laudanosine in a group of acute renal failure patients undergoing IPPV and to compare this route of clearance with that in the urine.

PATIENTS AND METHODS

Ethics Committee approval was obtained for this study and informed written consent obtained from the patient's next-of-kin before sample

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TABLE 1. Clinical details of the 15 patients. Atrac. = Atracurium; SLE = systemic lupus erythematosus; Dop = dopamine; Dob = dobutamine; NA = noradrenaline; A = adrenaline

Patient No.	Sex	Age (yr)	Wt (kg)	Diagnosis	Admission APACHE score	Duration of atrac. infusion (h)	Creatinine clearance (ml min ⁻¹)	Inotropic agents
Group 1								
1	M	37	60	Atypical pneumonia	23	121	40	Dop, Dob
2	M	42	70	Gastro-intestinal haemorrhage	22	72	98	Dop
3	M	64	85	Aortic aneurysm repair	27	173	72	Dop, Dob, NA
4	M	39	80	Near drowning	21	210	103	Dop, Dob
5	F	66	75	Gram-ve septicaemia	11	64	94	Dop, Dob, A
6	F	39	65	Respiratory failure (SLE)	12	41	40	Dop
7	M	52	140	Gastro-intestinal haemorrhage	22	305	108	Dop, Dob, NA
8	M	53	80	Myocardial infarct	21	24	100	Dop, Dob
Group 2								
9	M	64	70	Aortic aneurysm repair	37	37		Dop, Dob, NA
10	F	58	70	Gram-ve septicaemia	22	112		Dop, Dob, NA
11	M	56	75	Viral myocarditis	28	93		Dop, Dob, NA, A
12	M	49	80	Aortic aneurysm repair	31	182		Dop, Dob, NA, A
13	M	62	90	Oesophago-gastrectomy	24	288		Dop, Dob, NA, A
14	M	30	70	Acute pancreatitis	21	617		Dop, Dob, NA
15	M	38	70	Pneumococcal pneumonia	30	266		Dop, Dob, NA

collection. We studied eight patients undergoing IPPV with normal renal function (mean creatinine clearance = 81 ml min⁻¹, range 40–110 ml min⁻¹) (group 1) and seven patients in acute renal failure on IPPV who were undergoing CVVH with a creatinine clearance of less than 5 ml min⁻¹ (group 2). All were receiving constant infusions of atracurium 0.3–0.8 mg kg⁻¹ h⁻¹ in addition to analgesia and sedation with constant i.v. infusions of morphine 2–10 mg h⁻¹ and midazolam 2–10 mg h⁻¹ as indicated clinically. Clinical details of the patients are given in table 1. All those in group 1 had an indwelling urinary catheter as part of their clinical management.

Blood 5 ml was taken from an arterial cannula at least every 4 h during infusion of the drug for measurement of plasma concentrations of atracurium and laudanosine. In patients in group 1,

urine 5 ml was collected from the connection of the bladder catheter to the urine collecting bag at the same time as the blood sample. The volume of urine produced in the next 60 min was noted and the urine flow derived (ml min⁻¹). Blood was collected at similar intervals from the patients in group 2 when they were receiving CVVH. Haemofiltration fluid 5 ml was collected simultaneously from the exit port of the dialysis machine (Gambro AK 10 system with FH66 fibre haemofilters). The blood flow through the filter was maintained at 125 ml min⁻¹ and the outflow from the filter restricted to give an average haemofiltrate flow of 19 ml min⁻¹ (27.4 litre day⁻¹).

The plasma samples were assayed in this department as described previously [5]. Immediately after collection, specimens of urine (50 µl)

TABLE II. Mean plasma, urine (group 1) and haemofiltrate (HF) (group 2) concentrations of atracurium and laudanosine measured at steady state in each patient, together with the urine flow rate and atracurium infusion rate. (The haemofiltrate flow rate was fixed at 19 ml min⁻¹)

Patient No.	No. of steady state samples	Atracurium concn (ng ml ⁻¹)		Laudanosine concn (ng ml ⁻¹)		Urine flow rate (ml kg ⁻¹ min ⁻¹)	Infusion rate (μg kg ⁻¹ min ⁻¹)
		Plasma	Urine or HF	Plasma	Urine or HF		
Group 1							
1	7	711	35787	804	4818	0.016	6
2	4	1239	19622	1290	12207	0.065	10
3	16	1514	15555	3245	31544	0.03	10
4	5	2103	23076	3281	31242	0.026	18
5	6	1245	8896	3174	40412	0.016	10
6	7	1888	6380	2312	30350	0.035	9
7	23	1827	126712	3203	98808	0.02	10
8	4	1577	58301	2096	48339	0.014	10
Group 2							
9	5	1261	387	1009	310		10
10	5	1745	1072	1510	899		10
11	7	1786	608	1386	409		7
12	9	1122	319	1234	510		10
13	20	1259	642	1894	644		7
14	7	2349	359	1563	481		10
15	7	1437	1173	3185	1083		7

and haemofiltrate (200 µl) were added to 1.5-ml microtest tubes containing potassium hydrogen phthalate buffer 950 µl and 800 µl, respectively; the pH had previously been adjusted to 2.5. The tubes and contents were frozen in liquid nitrogen and stored at -20 °C. The urine and haemofiltrate samples were assayed using the same HPLC technique as that used for the plasma specimens.

After the samples were analysed and it was determined which were recorded when plasma concentrations of both atracurium and laudanosine were at steady state, the corresponding plasma, urine and haemofiltration samples were used to derive the appropriate clearance values. Steady state was accepted as four consecutive plasma samples showing a variation in plasma concentration of less than 15 %. The steady state plasma clearances (Cl_p) of atracurium were derived using the formula:

$$Cl_p = \frac{\text{Infusion rate (ng kg}^{-1} \text{ min}^{-1})}{C_p^{ss} \text{ (ng ml}^{-1})}$$

where C_p^{ss} = steady state plasma concentration.

For laudanosine, the infusion rate was calculated by assuming that one molecule of atracurium eventually breaks down to yield two molecules of laudanosine [6].

The urinary clearance for each set of estimations was derived using the formula UV/P , where U =

urinary concentration (ng ml⁻¹), V = urinary flow rate (ml min⁻¹) and P = plasma concentration (ng ml⁻¹). The clearance achieved with CVVH was derived using the Sieving coefficient, S :

$$Cl = S \times HF$$

where HF = haemofiltrate flow (ml min⁻¹), the Sieving coefficient being derived from the ratio of the haemofiltrate to plasma concentration, as described by Golper and others [7].

The mean plasma clearances of atracurium and laudanosine in groups 1 and 2 were compared using the Mann-Whitney U test.

RESULTS

The mean plasma, urine and haemofiltrate concentrations of atracurium and laudanosine for each patient in groups 1 and 2, and the number of paired samples collected from each patient are shown in table II.

The mean (SD, range) plasma clearances of atracurium and laudanosine at steady state in group 1 patients are shown in table III, with the mean urinary clearances of the two substances. The renal clearances of atracurium and laudanosine were approximately 8 % and 9 % of the plasma clearances, respectively.

The mean plasma clearances of atracurium and laudanosine in the renal failure patients (group 2)

TABLE III. Mean (SD) [range] plasma clearances of atracurium and laudanosine for the two groups; urinary clearances in group 1 and CVVH clearances in group 2. No significant differences (Mann-Whitney U test) between the two groups in the plasma clearances of either substance

	Atracurium clearance (ml kg ⁻¹ min ⁻¹)		Laudanosine clearance (ml kg ⁻¹ min ⁻¹)	
	Plasma	Urine or CVVH	Plasma	Urine or CVVH
Group 1	7.1 (1.4) [4.8–8.6]	0.55 (0.5) [0.11–1.4]	3.8 (1.5) [2.4–6.0]	0.33 (0.2) [0.10–0.62]
Group 2	6.7 (1.8) [4.6–8.9]	0.11 (0.06) [0.06–0.2]	4.5 (1.8) [2.8–7.4]	0.09 (0.02) [0.06–0.14]

are also shown in table III, with the mean notional haemofiltration clearances. The haemofiltration clearances of atracurium and laudanosine were only 1.6% and 2% of the plasma clearances, respectively.

There was no significant difference in the plasma clearances of atracurium and laudanosine between the two groups.

DISCUSSION

Work in cats first demonstrated that not all of a bolus dose of atracurium is degraded in the plasma: 6.9% is excreted in the urine [8]. In the first human study (1987), it was estimated that the amount of atracurium and laudanosine excreted in the urine over a period of 500 min after a bolus dose of the drug, given to three healthy, uncatheterized patients, was 2–10% [9]. No precautions could be taken to prevent further breakdown of atracurium in the urine present in the bladder in this study. More recent work by Vandembrom, Wierda and Agoston on the pharmacokinetics of a bolus dose of atracurium, which included measurement of urinary clearance in catheterized patients, has supported the earlier findings [10].

The urinary clearances reported here are the first estimated at steady state. The mean urinary clearance of atracurium (0.6 ml kg⁻¹ min⁻¹; 8% of the plasma clearance) may be an underestimate, for atracurium breakdown may be assumed to have continued in the urine as it passed down the ureter and through the bladder. This continued degradation tended to reduce the value for the urinary concentration of atracurium (*U*), thus decreasing the clearance value. In contrast, the urinary concentration of laudanosine must have been increased by the same process; thus the actual urinary clearance of laudanosine should be slightly less than that reported here (0.3 ml kg⁻¹ min⁻¹; 9% of the plasma clearance). The urinary

clearances of both atracurium and laudanosine are much less than those of plasma and are probably of limited clinical significance, certainly when atracurium is used as a bolus dose during general anaesthesia. However, the relevance of this route of excretion when the drug is given for hours, even days, by constant infusion in the intensive care unit is more difficult to assess.

Intensive care patients with "normal" renal function have lower creatinine clearances (mean 80 ml min⁻¹) than those of truly healthy individuals, although the difference is of little clinical significance. Renal clearance of atracurium and laudanosine during anaesthesia in healthy subjects may be expected to be greater than that reported here, but renal function during anaesthesia is usually impaired, especially during the first 60 min, and is probably not dissimilar to that found in the intensive care patient [11].

It is interesting that the plasma clearances of both atracurium and laudanosine in the more critically ill patients with renal failure were similar to those in the patients with normal renal function—findings which are compatible with those reported previously by Parker, Jones and Hunter, who used a method which did not rely on achievement of a steady state [12]. Although it has been demonstrated that the use of high doses of inotropic agents such as dopamine, dobutamine, noradrenaline and adrenaline (as used in our patients in group 2) may constrict hepatic blood flow, thus reducing hepatic metabolism of other drugs [13], there is no evidence in this study to suggest that the clearance of each substance was decreased in these ill patients.

When elimination of drugs by CVVH (or haemodialysis) is considered, only plasma protein binding and volume of distribution have been shown to be important, although these measures are not totally reliable indicators of drug clearance [14]. The haemofiltrate composition is essentially the same as that of plasma water. Thus it may be

expected that drugs which are highly protein bound or have large volumes of distribution (and are therefore found only in low concentrations in the plasma water compartment)—for example propranolol—would be cleared poorly by CVVH [14]. The protein binding of atracurium is not known for certain, although a value of 80% has been obtained by an indirect method [15]. This relatively high degree of binding, coupled with a volume of distribution in the range 172–280 ml kg⁻¹ [5, 10], would suggest only limited elimination of atracurium by CVVH and, indeed, this was found to be the case in our study. The volume of distribution of the more lipophilic laudanosine is much greater (1730 ml kg⁻¹ [15]), which would imply even less clearance of the metabolite by CVVH, although this study does not substantiate such a hypothesis.

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REFERENCES

1. Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD. Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. *Anesthesiology* 1986; 65: 6–12.
2. Campbell IT, Baxter JN, Tweedie IE, Taylor GT, Keens SJ. I.v. fluids during surgery. *British Journal of Anaesthesia* 1990; 65: 726–729.
3. Sweny P. Haemofiltration and haemodiafiltration—theoretical and practical aspects. *Current Anaesthesia and Critical Care* 1991; 2: 37–43.
4. Golper TA, Pullian J, Bennett WM. Removal of therapeutic drugs by continuous arteriovenous hemofiltration. *Archives of Internal Medicine* 1985; 145: 1651–1652.
5. Kent AP, Parker CJR, Hunter JM. The pharmacokinetics of atracurium and laudanosine in the elderly. *British Journal of Anaesthesia* 1989; 63: 661–666.
6. Stiller RL, Ryan Cook D, Chakravorti S. *In vitro* degradation of atracurium in human plasma. *British Journal of Anaesthesia* 1985; 57: 1085–1088.
7. Golper TA, Wedel SK, Kaplan AA, Saad A-M, Donta ST, Paganini EP. Drug removal during continuous arteriovenous haemofiltration: theory and clinical observations. *International Journal of Artificial Organs* 1985; 8: 307–312.
8. Neill EAM, Chapple DJ. Metabolic studies in the cat with atracurium: A neuromuscular blocking agent designed for non-enzymatic inactivation at physiological pH. *Xenobiotica* 1982; 12: 203–210.
9. Ward S, Boheimer N, Weatherley BC, Simmonds RJ, Dopson TA. Pharmacokinetics of atracurium and its metabolites in patients with normal renal function and in patients in renal failure. *British Journal of Anaesthesia* 1987; 59: 697–706.
10. Vandembrom RHG, Wierda JMKH, Agoston S. Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clinical Pharmacokinetics* 1991; 19: 230–240.
11. Deutsch S, Bastron RD, Pierce EL, Vandam LD. The effects of anaesthesia with thiopentone, nitrous oxide, narcotics and neuromuscular blocking drugs on renal function in normal man. *British Journal of Anaesthesia* 1969; 41: 807–815.
12. Parker CJR, Jones JE, Hunter JM. Disposition of infusions of atracurium and its metabolite, laudanosine, in patients in renal and respiratory failure in an ITU. *British Journal of Anaesthesia* 1988; 61: 531–540.
13. Benowitz N, Forsyth RP, Melmon KL, Rowland M. Lidocaine disposition kinetics in monkey and man. II: Effects of hemorrhage and sympathomimetic drug administration. *Clinical Pharmacology and Therapeutics* 1974; 16: 99–109.
14. Keller F, Wilms H, Schultze G, Offerman G, Molzahn M. Effect of plasma protein binding, volume of distribution and molecular weight on the fraction of drugs eliminated by haemodialysis. *Clinical Nephrology* 1983; 19: 201–205.
15. Foldes FF, Deery A. Protein binding of atracurium and other short acting neuromuscular blocking agents and their interaction with human cholinesterases. *British Journal of Anaesthesia* 1983; 55: 315–345.

INTRAOPERATIVE ASSESSMENT OF ATRACURIUM-INDUCED NEUROMUSCULAR BLOCK USING DOUBLE BURST STIMULATION†

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SUMMARY

Paired train-of-four (TOF) and double burst stimuli (DBS) were administered to the ulnar nerve at the wrist in 25 patients (group 1) paralysed with atracurium 0.5 mg kg⁻¹; responses were measured mechanically (except every third DBS response which was manually evaluated). Another 30 patients (group 2) received a DBS every 60 s. A post-tetanic count (PTC) was performed when the first response (D1) was palpated. There was a significant correlation between the twitch heights of the first TOF response (T1) and D1 and likewise between the twitch heights of both second responses ($r = 0.9$; $P < 0.001$), but there was a significant difference in regression coefficients of these two correlations ($P < 0.001$). D1 was palpable first with a median PTC of 7. Our results showed that palpation of a single response implied a satisfactory level of paralysis. DBS may be useful for intraoperative clinical monitoring of neuromuscular block.

KEY WORDS

Measuring techniques: neuromuscular block. Monitoring: neuromuscular function. Neuromuscular relaxants: atracurium.

Train-of-four (TOF) peripheral nerve stimulation with tactile assessment of response is used widely for monitoring neuromuscular block. However, it is inaccurate for identifying residual block [1] and has been shown recently not to influence the total dose of relaxant used or the incidence of postoperative residual neuromuscular block [2].

Double burst stimulation (DBS) is the most reliable clinical method of detecting residual

paralysis [3], but its suitability for quantifying profound and intermediate levels of neuromuscular block is not clear. We have therefore investigated its potential for this use.

PATIENTS AND METHODS

The study was approved by the Hospital Research Ethics Committee, but in view of the routine nature of neuromuscular monitoring, patient consent was not sought. We studied 55 healthy adult patients, none of whom was receiving any medication which may have influenced neuromuscular transmission.

All patients were anaesthetized in a standard manner. After premedication with papaveretum and hyoscine, anaesthesia was induced with propofol 2-3 mg kg⁻¹ i.v. and maintained with 1% enflurane (after an initial overpressure period of 3 min with 5% enflurane) and 66% nitrous oxide in oxygen. Neuromuscular block was produced with atracurium 0.5 mg kg⁻¹ and subsequent increments of 0.2 mg kg⁻¹ were given according to clinical need. Fentanyl 50-100 µg i.v. was administered for analgesia as required. Normocapnia (based on end-tidal carbon dioxide measurement) was maintained throughout the study using positive pressure ventilation via a tracheal tube or laryngeal mask airway. The ulnar nerve was stimulated at the wrist with a Rutter

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†A preliminary account of this work was presented at the Anaesthetic Research Society meeting, Edinburgh, November 1990.

MkV programmable nerve stimulator via surface electrodes on the side opposite to which i.v. access and an arterial pressure cuff were sited.

The patients were allocated to two groups. In group 1 the force of the isometric adductor pollicis contraction was measured using a Grass FT-10 force displacement transducer [4], Lectromed MX 216 amplifier and chart recorder. After a stabilization period of 3–5 min after induction, the supramaximal point and control values were established using a 1-Hz stimulus. Thereafter, a set stimulus sequence was delivered to the patient every 120 s for the remainder of the study. This consisted of a TOF stimulus followed 20 s later by a DBS [3]. Before every third DBS, the thumb mount was disconnected from the transducer and one of five observers (each familiar with the use of a nerve stimulator) palpated the thumb response to stimulation. This response was recorded as no response, single response or double response. The same observer was used throughout any single patient study. The recorded level of block was concealed from the observer, who was also unaware of whether or not any incremental dose of atracurium had recently been administered. A 200-g resting abducting tension on the thumb was maintained throughout the study and this was confirmed before each recording and after reconnection. Readings taken during the 6 min following administration of incremental doses of atracurium were discounted.

After completion of an individual patient study, the amplitude of the first twitch of each TOF response (T1) was measured from the paper record and expressed as a fraction of the measured control value (T1/C). T1/C values of more than 0.55 were considered to lie outside the range of adequate surgical relaxation and were excluded. Each T1/C value before and after palpation was compared. Measured values where T1/C was less than 0.03 were excluded from the data, because of their low signal-to-noise ratio. The first, third and fifth readings occurring subsequently were selected from each patient's data, in order to include a wide range of block and to exclude bias towards those patients undergoing longer operations. These were compared with their respective first and second DBS (D1 and D2) twitch height measurements. In each case the following comparisons were made: T1/C with the ratio D2:D1; D1 with T1 twitch heights; and D2 with T2 twitch heights (where present). The first, median and last palpated DBS responses were also

selected and compared with their paired T1/C values.

In group 2, the supramaximal point was established by palpation by one of two observers. A similar DBS pattern to that used previously was delivered every 60 s and a PTC was performed 20 s after the first D1 response became palpable. The median PTC and range of the 30 data points were computed.

Data were expressed as mean (sd) or median (range). The relationships of twitch heights of T1 with D1 and T2 with D2 were compared using linear regression analysis. The difference between regression coefficients was evaluated with reference to tables of normal distribution. $P < 0.05$ was considered significant.

RESULTS

Twenty-five patients were studied in group 1. The mean age was 46.5 yr (range 17–74 yr), the male:female ratio 1.4:1 and the median duration of each study was 39 (17–65) min. Because of a prolonged period of profound block (no response to DBS or TOF) or short operative time, insufficient palpation data were gained from six patients and insufficient measurement data from five patients. These patients were excluded from the relevant data groups.

D1 always returned before T1 on 18 occasions when profound block was achieved. All T1 readings taken after palpation were 2–8% greater than the T1 reading taken before palpation. From the 60 measured readings selected, a significant linear correlation between D1 and T1 (fig. 1) was evident ($r = 0.9$; $P < 0.001$; regression coefficient

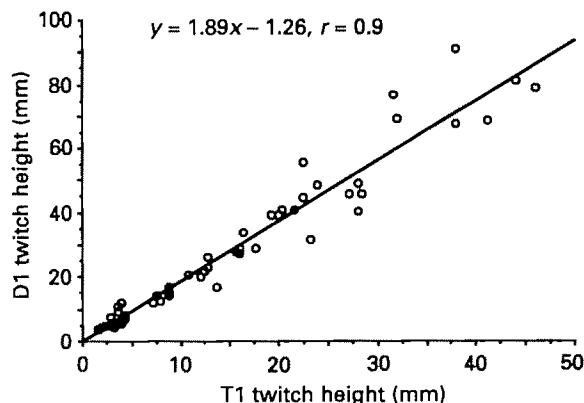


FIG. 1. Relationship between the measured twitch heights of T1 and D1, showing the line of best fit.

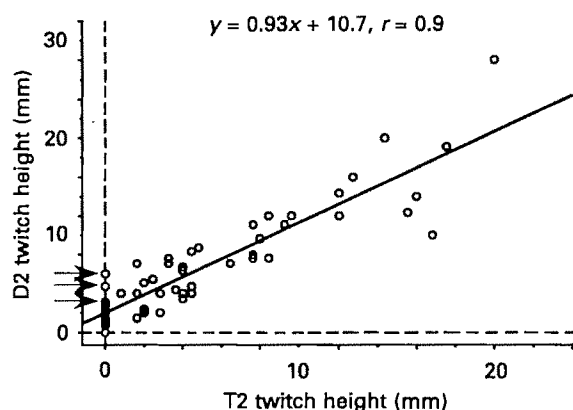


FIG. 2. Relationship between the measured twitch heights of T2 and D2, indicating the line of best fit. Note the difference in scale between the axes of this graph and those of figure 1. The arrowed data points are derived from three patients (see text).

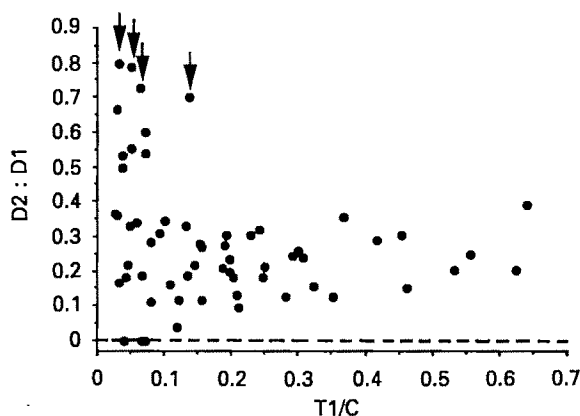


FIG. 3. D2:D1 ratio at different degrees of neuromuscular block (indicated by T1/C). The arrowed data points are derived from three patients (see text).

1.89). There was a similar degree of correlation between D2 and T2 twitch heights ($n = 57$; $r = 0.9$; regression coefficient 0.93) (fig. 2). The two data set regression coefficients differed significantly ($P < 0.001$). Figure 2 shows that when no T2 response was present there was a particularly wide scatter of D2 twitch heights.

There was poor correlation between D2:D1 and T1/C ($r = 0.3$), with data points particularly widely scattered through the range of T1/C 0–0.1 (fig. 3).

Fifty-seven palpated DBS responses were selected, of which 27 were perceived as a single response and 30 as a double response. The relationship between these responses and different levels of neuromuscular block is indicated in figure 4. Only one double response was palpated when T1/C was < 0.05 and two responses were always palpated when T1/C > 0.20 . Thus palpation of a single response implied a T1/C of < 0.20 ($P = 1$), but palpation of a double response implied only a 0.66 chance of T1/C ≥ 0.20 . Palpation of a double response did, however, suggest a 0.97 chance of T1/C ≥ 0.05 . The sensitivity of this technique in identifying a T1/C value above or below 0.20 was 0.73 and the specificity was 1. The arrowed data points in figures 2–4 were derived from the same three patients and illustrate an earlier and relatively more powerful initial return of D2. There was no common observer or demographic factor link between these patients.

The mean age of the 30 patients studied in group 2 was 45.3 yr (range 20–77 yr) with the male:female ratio 1:1.3. Data from this group indicated a median PTC when D1 was first palpated of 7 (3–12).

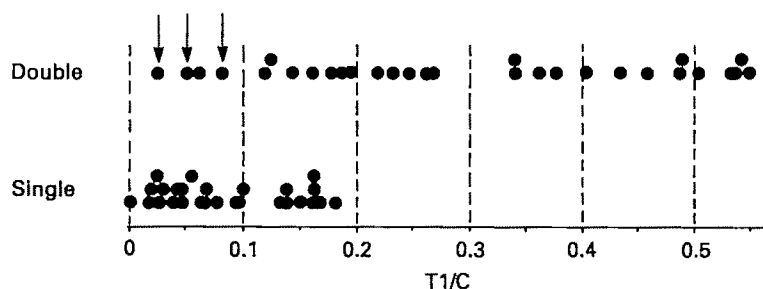


FIG. 4. Number of single and double palpated responses at different degrees of neuromuscular block. The arrowed data points are derived from three patients (see text).

DISCUSSION

The three elements of the D1 stimulus produced a more powerful response than the single T1 response by a factor of almost 2 (fig. 1); this would suggest easier and earlier recognition of the D1 DBS response. This is confirmed by our other results: D1 always returned before T1 and the median PTC when D1 was first palpated was 7 (compared with a PTC of 8–14 using the TOF [5, 6]). Our PTC result probably overestimates the true value, as a 60-s interval elapsed between assessments and our D1 response was palpated, not visualized as in the study by Bonsu and colleagues [5]. This result is also consistent with other published work which has shown that D1 returns 2.2 min earlier than T1 [7].

The relationship between T2 and D2 differed significantly from that between T1 and D1 (as shown by the slopes of the regression lines in figures 2 and 3). Despite the greater power of the D2 electrical stimulus, the D2 response was similar in force to T2, although D2 did return at an earlier stage in recovery of neuromuscular function. The reason for this is unclear, but may reflect enhanced fade after the D1 stimulus.

The poor correlation between D2:D1 and T1/C (fig. 3) may reflect the fact that these parameters quantify different aspects of the effect of atracurium on neuromuscular function (in a manner analogous to the relationship between T4/T1 and T1/C). Fade is a presynaptic phenomenon and attenuation of a single response has a postsynaptic basis [8]. The scatter is particularly evident in the region of profound block, which may also partly reflect a reduced signal-to-noise ratio. The palpated responses mirror the wide interpatient measured variations in initial D2 recovery. In figures 2–4 the data points where D2 returned relatively early or more powerfully (indicated by arrows) were derived from the same three patients in whom D2 response was palpated at a relatively early stage in recovery of neuromuscular function (fig. 4). These patients appear to represent the extremes of the spectrum, rather than a discrete group and have contributed to the reduced sensitivity of the DBS response with profound block.

Our palpated results indicated satisfactory specificity, but less satisfactory sensitivity for DBS as a test to identify a T1/C of less than 0.05 or more than 0.20. Identification of these points is of particular clinical value: a T1/C value of less

than 0.20–0.25 is compatible with adequate intra-operative relaxation when a volatile agent is used [9] and excellent conditions for tracheal intubation are present with a T1/C value of less than 0.05 [10]. In addition, antagonism of atracurium-induced paralysis may be accomplished reliably from this latter point in less than 9.6 min [11]. Nevertheless, despite limitations of sensitivity, palpation of a single response implies a T1/C value < 0.20 and palpation of a double response a T1/C value ≥ 0.05 with a high degree of certainty.

The clinical use of the TOF stimulus pattern (and likewise DBS) during operation is based on a fade-induced reduction in the number of responses relating reliably to the degree of attenuation of T1 [12]. This close relationship between the pre- and postsynaptic effects has been shown to be present with atracurium and an anaesthetic technique similar to our own [13]. However, the same workers in another study using vecuronium have shown a considerably wider variation in *visual* assessment of T2 return (T1/C of 0.16 (SD 0.1)) compared with *measured* assessment [13, 14]. This discrepancy may result from difficulty in interpreting up to four responses and could account for the limited impact of TOF usage in clinical practice [2].

DBS used for the quantification of the attenuated T1 response is based probably on the same pre- and postsynaptic mechanisms, but may be complicated by enhanced D2 fade (see above), resulting in more interpatient variation than TOF. Nevertheless, it is possible that the simplicity of the double DBS response may offer enhanced clinical accuracy in comparison with TOF.

Validity of data could have been impaired by variations in neuromuscular junction temperature, changes in the resting tension of the adductor pollicis muscle or alterations in the neuromuscular effects of enflurane (compared with initial control value). Although temperature was not measured, the effect of this was likely to be very limited as surgery was of a minor nature, all i.v. infusions were delivered through the opposite arm and the duration of the studies was relatively short. The resting tension was confirmed as being unchanged throughout the study and the 2–8% increase in T1 values after reconnection of the thumb almost certainly reflects spontaneous recovery of block over the 2-min period between consecutive readings. The neuromuscular effect of enflurane is related to blood concentration and period of exposure [15]. The effect of consistent over-

pressuring at the outset and the short duration of each study would thus have limited the influence of this variable.

In conclusion, our data and the results of others show that DBS may be used as a universal stimulus pattern throughout the full range of neuromuscular block. Palpation of a single response may reliably indicate adequate intraoperative relaxation, but palpation of a double response does not necessarily imply adequate relaxation. DBS, however, may detect initial return of neuromuscular function earlier than TOF. Measurements of DBS response confirmed an enhancement of D1 response compared with T1, but showed an unexpected relative impairment of D2 response compared with T2. This study suggests that the simpler double response of DBS may offer a clinical advantage in comparison with TOF in the accuracy of monitoring neuromuscular function at levels of block suitable for intraoperative use.

REFERENCES

1. Viby-Mogensen J, Jensen NH, Engbæk J, Ording H, Skovgaard LT, Chraemmer-Jorgensen B. Tactile and visual evaluation of the response of train-of-four stimulation. *Anesthesiology* 1985; 63: 440-443.
2. Pedersen T, Viby-Mogensen J, Bang U, Olsen NV, Jensen E, Engbæk J. Does perioperative tactile evaluation of the train-of-four response influence the frequency of postoperative residual neuromuscular blockade? *Anesthesiology* 1990; 73: 835-839.
3. Drenck NE, Ueda N, Olsen NV, Engbæk J, Jensen E, Skovgaard LT, Viby-Mogensen J. Manual evaluation of residual curarization using double burst stimulation: A comparison with train-of-four. *Anesthesiology* 1989; 70: 578-581.
4. Ali HH, Saverese JJ. Monitoring of neuromuscular function. *Anesthesiology* 1976; 45: 216-249.
5. Bonsu AK, Viby-Mogensen J, Fernando PUE, Muchal K, Tamilarasan A, Lambourne A. Relationship of post-tetanic count and train-of-four response during intense neuromuscular blockade caused by atracurium. *British Journal of Anaesthesia* 1987; 59: 1089-1092.
6. Ridley SA, Hatch D. Post-tetanic count and profound neuromuscular blockade with atracurium infusion in paediatric patients. *British Journal of Anaesthesia* 1988; 60: 31-35.
7. Gill SS, Donati F, Bevan DR. Clinical evaluation of double-burst stimulation: Its relationship to train-of-four. *Anaesthesia* 1990; 45: 543-548.
8. Bowman WC. Prejunctional and postjunctional cholinergic receptors at the neuromuscular junction. *Anesthesia and Analgesia* 1980; 59: 935-941.
9. Ali HH, Miller RD. Monitoring of neuromuscular function. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone, 1986; 876-878.
10. Donlon JV jr, Ali HH, Saverese JJ. A new approach to the study of four non-depolarizing relaxants in man. *Anesthesia and Analgesia* 1974; 53: 934-939.
11. Astley BA, Hughes R, Payne JP. Antagonism of atracurium-induced neuromuscular blockade by neostigmine or edrophonium. *British Journal of Anaesthesia* 1986; 58: 1290-1295.
12. Lee C. Train-of-4 quantitation of competitive neuromuscular block. *Anesthesia and Analgesia* 1975; 54: 649-653.
13. O'Hara DA, Fragen RJ, Shanks CA. Reappearance of the train-of-four after neuromuscular blockade induced with tubocurarine, vecuronium or atracurium. *British Journal of Anaesthesia* 1986; 58: 1296-1299.
14. O'Hara DA, Fragen RJ, Shanks CA. Comparison of visual and measured train-of-four recovery after vecuronium-induced neuromuscular blockade using two anaesthetic techniques. *British Journal of Anaesthesia* 1986; 58: 1300-1302.
15. Stanski DR, Ham J, Miller RD, Sheiner LB. Time dependent increase in sensitivity to dTC during enflurane anesthesia. *Anesthesiology* 1979; 51: S269.

ALCOHOL AFTER SEDATION WITH I.V. MIDAZOLAM-FENTANYL: EFFECTS ON PSYCHOMOTOR FUNCTIONING†

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SUMMARY

Patients who arrive home several hours after outpatient surgery may drink alcohol. The extent to which residual drugs used in outpatient surgery interact with alcohol is not known. The purpose of this study was to determine if two i.v. drugs commonly used together in outpatient surgery, midazolam and fentanyl, have residual effects which would interact with alcohol drunk 4 h after injection. Twelve healthy male volunteers participated in a double-blind, randomized, placebo-controlled and cross-over study. Subjects were studied four times successively with a period of 1 week between trials. On each day of testing, the subjects received randomly, by slow i.v. injection (30 s), either saline followed immediately by saline, or midazolam 0.1 mg kg⁻¹ followed immediately by fentanyl 2 µg kg⁻¹. Four hours after the injection, the subjects consumed a beverage which either did or did not contain alcohol 0.7 g kg⁻¹. Before and 1, 3, 5 and 7 h after injection (and before and 1 and 3 h after consumption of beverage), psychomotor performance and mood were assessed. While both the combination midazolam-fentanyl and alcohol had independent effects on the dependent measures in this study, there was no interaction between midazolam-fentanyl and alcohol (no potentiating of effects of alcohol by i.v. sedation). We conclude that the effects of benzodiazepines and opioids that are short-acting and used in outpatient surgery have probably dissipated by the time a patient arrives home, and that effects from alcohol ingested at home will probably not be affected by recent administration of these drugs.

KEY WORDS

Alcohol: psychomotor function. Anaesthesia: day care. Analgesics: fentanyl. Hypnotics, benzodiazepines: midazolam.

The number of outpatient operations is increasing [1, 2]. In order to be ready for discharge, patients must be able to dress and walk without assistance. This does not imply that they can safely drive, cook, or care for small children. Despite being told not to, some patients drive or even drink alcohol [3]. It is important, therefore, to understand the residual effects of drugs used commonly in outpatient surgery or endoscopy and the extent to which these residual effects interact with alcohol. Many of the drugs used in outpatient surgery for analgesia or sedation are known to impair various psychomotor functions well after the patient is discharged from hospital [4].

There are many studies demonstrating that the psychomotor impairing effects of alcohol are potentiated by benzodiazepines when the two substances are given in combination [5-10]. However, there is only one study to date which has examined any interactions when alcohol was given several hours after i.v. sedation [11]. In our study, we sought to determine if fentanyl given in combination with midazolam would potentiate

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the effects of psychomotor and cognitive functioning of alcohol consumed several hours later.

SUBJECTS AND METHODS

We studied 12 healthy males (mean age 23.0 yr (range 21–30 yr); weights 78.5 (SD 11.9) kg; heights 181.2 (7.5) cm) with a history of recreational use of alcohol. The study was approved by our Board of Institutional Review and informed written consent was obtained from subjects before the first session. An anaesthetist performed a history and physical examination. Subjects were excluded if they had an adverse experience with general or i.v. anaesthesia, or sedation/analgesia, or had any systemic disease. Persons eligible for the study were not permitted to take medication that was prescription or over-the-counter during the 3 weeks of the study. Subjects fasted before the testing sessions and did not drink alcohol for 24 h before sessions. Abstinence from alcohol was verified by measuring the concentration of blood alcohol when the subject arrived for each session. Subjects were paid £196 (\$350 U.S.) for their participation upon completion of the study.

The study was double-blind, randomized and cross-over. Each subject was tested on four different test sessions at intervals of 1 week. Subjects received i.v. injections of either midazolam 0.1 mg kg⁻¹ followed immediately by fentanyl 2 µg kg⁻¹, or saline followed by saline, using the same volumes of saline as active drug. The time for injection for each drug was 30 s. Four hours later the subjects consumed a beverage that either did or did not contain alcohol 0.7 g kg⁻¹. The doses of midazolam and fentanyl used are those given usually during outpatient procedures for this age group. The dose of alcohol used is approximately equivalent to 1.4 litre of beer, 950 ml of wine or 180 ml of spirits and would be expected to increase the blood concentration of alcohol to approximately 0.6 ml dl⁻¹ in a fasted, 70-kg male. The lemonade-and-lime flavoured beverages that contained alcohol had 10% ethyl alcohol by volume in a volume of 450 ml (per 70 kg). Beverages were served cold in cups. Subjects had 20 min to consume the beverage.

Before the first session of the experiment, subjects were trained (three practice sessions) to use the apparatus in order to prevent further learning of the tasks during actual testing. Evaluation of psychomotor performance and subjective effects (see below) were performed before and 1,

3, 5 and 7 h after i.v. sedation. Blood concentrations of alcohol were measured before and 5 and 7 h after i.v. sedation (1 and 3 h after consumption of beverage). A snack was served approximately 2 h after injection of drug, and lunch was served to subjects approximately 6 h after injection (1.5 h after alcohol ingestion).

Psychomotor effects, mood and blood concentrations of alcohol were the dependent measures in this study. These measures took approximately 25 min to complete and were performed always in the same order. The Maddox wing test was used to measure eso- and exophoria (motor function of the eyes) [12]. An action judgement tester, similar to a test of driving, was used: with a steering wheel, subjects attempted to keep two pointers on a moving track without striking objects; number of mistakes (when pointers struck objects) was recorded. Body sway was measured using a strain gauge that was computerized: subjects stood on a force plate for 60 s with their eyes closed and variations in movement in the antero-posterior and lateral direction were recorded. A critical flicker fusion test (CFFT) was used to measure changes in overall integrative activity of the CNS (the CFFT has been shown to be sensitive to the effects of fentanyl [13]). Subjects first performed three ascending series of trials (from flicker to fusion) and then three descending series of trials (fusion to flicker).

Subjects performed four psychomotor tests on a computer. Simple auditory and visual reaction times were determined by measuring the time it took the subject to press a button after hearing a sound or seeing a letter on the computer screen. Divided attention reaction time was determined in a test in which several stimuli were presented simultaneously in different sectors of the computer screen. The subject had to press the appropriate key when a certain target stimulus appeared in a background of false stimuli; the test was run at supramaximal speed so it was impossible to react to all stimuli presented. Number of responses that were correct and incorrect were recorded also in this test. Eye-hand co-ordination was measured by the subject tracking a moving circle on a computer screen with a cross controlled by a "mouse". Mistakes of co-ordination were measured by counting the number of times that the cross exceeded a certain distance (1 cm) from the target circle. The duration (in seconds) that the cross exceeded 1 cm from the circle was also recorded. Accuracy of co-ordination was deter-

mined by measuring the mean distance (in pixels) between the cross and the target during the test.

Subjective effects were measured at baseline, and 1, 3, 5 and 7 h after injection of drugs with the Profile of Mood States (POMS). The POMS, chosen because it is sensitive to momentary mood states, consists of 72 adjectives used commonly to describe momentary mood states [14]. There is concordance as measured by the POMS scale of anxiety and two other standardized measures of "state" anxiety (Taylor Manifest Anxiety Scale, Spielberger State-Trait Anxiety Inventory) [15]. The POMS is the test used most often to quantify moods [16]. Subjects indicate how they feel at the moment in relation to each of these adjectives, from "not at all" (0) to "extremely" (4). Eight clusters of items have been derived using factor analysis and have been given names that best describe the clustered adjectives (anxiety, depression, anger, vigour, fatigue, confusion, friendliness and elation). In addition, two unvalidated scales (arousal and positive mood), shown previously to be sensitive to drug effects, were scored.

Blood concentration of alcohol was measured from breath air using an Alco-sensor 3-breath analyser (Intoximetrics Instruments, St Louis, MO, U.S.A.).

For each test, two repeated measures multivariate analyses of variance [17] were used. The first MANOVA studied the effects of drug (present or absent), using all five timepoints (hours 0, 1, 3, 5 and 7) in the analysis. The second MANOVA studied the effects of alcohol (present or absent), and the interaction of midazolam-fentanyl and alcohol, if any, using the hours 0, 5 and 7 after injection as timepoints (5 and 7 h after injection were equivalent to 1 and 3 h after ingestion). $P \leq 0.05$ was considered significant. *Post hoc* tests were used, when effects of significance of drug or alcohol were obtained, to determine the duration that psychomotor performance was impaired. We performed additional ANOVAs to determine if significant effects of learning were present by using week of testing as a factor.

RESULTS

Table I presents measures of psychomotor performance and subjective effects obtained before and 1 and 3 h after i.v. injection of either saline or midazolam-fentanyl. In the table, the four groups of study have been reduced to two: results for the groups of saline injection-placebo beverage and

saline injection-alcohol beverage have been averaged; and results for the groups of midazolam-fentanyl injection-placebo beverage and midazolam-fentanyl injection-alcohol beverage have been averaged. Tests in which drug effects of significance (or near significance) were obtained are presented. The injection of midazolam-fentanyl caused significant changes in eso/exophoria ($P < 0.05$) and increases in the number of mistakes made on the action judgement tester ($P < 0.05$). Body sway (antero-posterior) was increased significantly ($P < 0.05$) by the drug combination. Fusion-flicker threshold was also increased significantly by the drug combination ($P < 0.001$). Auditory reaction time ($P < 0.05$), divided attention ($P < 0.01$), and eye-hand co-ordination ($P < 0.005$) were impaired by midazolam-fentanyl. Scores of confusion from the POMS increased significantly after midazolam-fentanyl ($P < 0.05$). The effects of midazolam-fentanyl on fatigue ($P < 0.10$) and arousal ($P < 0.06$) approached significance. In general, the effects of impairing and sedating of midazolam-fentanyl had reached a peak 1 h after injection and approached baseline values 3 h after injection.

Mean (SD) blood concentration of alcohol 1 h after ingestion of alcohol (5 h after injection of drug or saline) was $0.65 (0.16) \text{ mg dl}^{-1}$ (frequently, a motorist with a blood concentration of alcohol of 1.0 mg dl^{-1} is considered to be driving under the influence of alcohol). Table II presents psychomotor performance and measures of subjective effects obtained at baseline (0 h) and 1 and 3 h after ingestion of beverage comprising either placebo or alcohol. In the table, the four groups of study have been reduced to two: results from the two groups receiving placebo (saline injection-placebo beverage and midazolam-fentanyl injection-placebo beverage) were averaged and the two groups receiving alcohol (placebo injection-alcohol beverage and midazolam-fentanyl injection-alcohol beverage) were averaged; tests are presented in which effects of significance (or near significance) of alcohol were noted. Alcohol caused significant impairment in visual reaction time ($P < 0.05$), eso/exophoria ($P < 0.01$), and eye-hand co-ordination ($P < 0.05$). These effects of alcohol reached a peak 1 h after ingestion and returned to baseline 2 h later. Alcohol tended to increase fatigue (0.07), elation (0.09) and positive mood (0.14), and decrease anger (0.07) and arousal (0.10). No significant learning took place during the study. There were no significant interactions

TABLE I. Psychomotor performance and measures of mood (mean (SD)) at baseline (0 h) and 1 and 3 h after injections of either saline or midazolam-fentanyl. § Significance (P value) is based on repeated measures multivariate analysis of variance comparing midazolam-fentanyl with saline, using hours 0, 1, 3, 5 and 7 as timepoints. Difference score (1 h-0 h) in mid-fentanyl injection condition significantly different from difference score (1 h-0 h) in saline injection condition: * P < 0.05; ** P < 0.01; *** P < 0.001. † Difference score from baseline (3 h-0 h) in mid-fentanyl injection condition significantly different (P < 0.05) from difference score from baseline (3 h-0 h) in saline injection condition. RT = Reaction time; CFFT = critical flicker fusion test; MDT = mean distance from target; POMS = profile of mood states

	Time after injection			P§
	0 h	1 h	3 h	
Saline injection				
Eso/exophoria (diopters)	1.85 (5.84)	1.96 (6.44)	2.17 (6.5)	
Action judgement (mistakes)	22.6 (14.4)	18.5 (12.4)	17.5 (10.7)	
Body sway				
Antero-posterior	692.5 (218.3)	764.1 (375.4)	831.4 (478.2)	
Lateral	651.2 (231.4)	681.7 (286.1)	706.0 (358.5)	
CFFT descend (Hz)	39.4 (6.1)	37.9 (7.1)	37.6 (7.6)	
Auditory RT (s)	0.285 (0.045)	0.295 (0.048)	0.284 (0.039)	
Divided attention RT (s)	0.546 (0.084)	0.533 (0.078)	0.531 (0.076)	
No. correct	90.0 (8.6)	91.9 (4.9)	91.5 (6.7)	
No. incorrect	10.7 (6.9)	10.1 (7.2)	10.1 (7.6)	
Eye-hand co-ord.				
No. mistakes	16.0 (5.7)	15.9 (5.6)	17.3 (6.0)	
Time off target (s)	4.08 (1.79)	3.98 (1.2)	5.09 (4.88)	
MDT (pixels)	10.8 (1.5)	10.7 (1.1)	12.0 (5.6)	
POMS (score)				
Fatigue	0.5 (0.568)	0.357 (0.509)	0.577 (0.725)	
Confusion	0.083 (0.41)	0.042 (0.443)	0.0 (0.326)	
Arousal	0.788 (0.972)	0.818 (1.07)	0.405 (1.23)	
Midazolam-fentanyl injection				
Eso/exophoria (diopters)	2.13 (6.01)	4.29 (6.83)*	3.71 (6.24)	0.05
Action judgement (mistakes)	16.5 (12.1)	40.0 (46.8)**	19.1 (14.4)†	0.05
Body sway				
Antero-posterior	647.7 (146.1)	1093.3 (453.7)***	759.4 (382.0)	0.05
Lateral	593.3 (167.4)	831.7 (359.1)*	587.3 (236.0)	0.08
CFFT descend (Hz)	38.4 (7.1)	33.3 (6.9)**	35.6 (7.6)	0.001
Auditory RT (s)	0.276 (0.041)	0.317 (0.05)**	0.291 (0.042)	0.05
Divided attention RT (s)	0.541 (0.071)	0.57 (0.085)**	0.535 (0.068)	0.01
No. correct	92.3 (4.1)	84.5 (10.7)***	89.4 (10.0)	0.01
No. incorrect	8.5 (4.7)	15.4 (10.9)**	12.4 (9.2)†	0.05
Eye-hand co-ord.				
No. mistakes	14.3 (4.9)	25.1 (13.5)***	17.7 (10.2)	0.001
Time off target (s)	3.46 (0.98)	8.69 (7.85)***	4.52 (2.9)	0.005
MDT (pixels)	10.7 (1.2)	14.4 (3.1)***	11.6 (2.0)	0.001
POMS (score)				
Fatigue	0.476 (0.531)	0.827 (0.739)**	0.708 (0.759)	0.10
Confusion	0.048 (0.392)	0.286 (0.374)**	0.131 (0.415)	0.05
Arousal	0.804 (0.991)	-0.127 (1.33)**	0.153 (1.28)	0.06

TABLE II. Psychomotor performance (mean (SD)) at baseline (0 h) and 1 and 3 h after either placebo or alcohol beverage (5 and 7 h after injection of saline or midazolam-fentanyl). § Significance (P value) is based on repeated measures multivariate analysis of variance comparing placebo with alcohol, using hours 0, 1 and 3 after ingestion of beverage (0, 5 and 7 h after injection) as timepoints. Difference score (1 h-0 h) in alcohol beverage condition significantly different from difference score (1 h-0 h) in placebo beverage condition: * $P < 0.05$; ** $P < 0.01$. † Difference score (3 h-0 h) in alcohol beverage condition significantly different (P < 0.05) from difference score (3 h-0 h) in placebo beverage condition. RT = Reaction time; MDT = mean distance from target; POMS = profile of mood states

	Placebo beverage			Alcohol beverage			P§
	0 h	1 h	3 h	0 h	1 h	3 h	
Visual RT (s)	0.315 (0.064)	0.303 (0.049)	0.291 (0.040)	0.303 (0.062)	0.344 (0.080)**	0.303 (0.042)	0.05
Eso/exophoria (diopters)	2.17 (5.84)	1.50 (6.44)	1.67 (6.5)	1.81 (6.01)	3.75 (6.83)**	2.92 (6.24)	0.01
Eye-hand co-ord.							
No. mistakes	14.1 (4.7)	15.9 (5.9)	14.2 (4.5)	16.3 (5.8)	23.5 (6.1)**	18.2 (6.5)	0.05
Time off target (s)	3.53 (1.02)	3.82 (1.31)	3.30 (0.92)	4.01 (1.80)	5.76 (1.65)**	4.30 (1.50)	0.05
MDT (pixels)	10.7 (1.0)	10.6 (1.1)	10.4 (0.8)	10.9 (1.6)	12.1 (1.4)**	10.9 (1.4)	0.01
POMS (score)							
Anger	0.104 (0.201)	0.100 (0.233)	0.146 (0.291)	0.132 (0.208)	0.125 (0.248)	0.073 (0.198)†	0.07
Fatigue	0.458 (0.597)	0.292 (0.418)	0.375 (0.447)	0.518 (0.496)	0.393 (0.535)	0.798 (0.961)†	0.07
Elation	1.08 (0.58)	0.83 (0.58)	0.88 (0.63)	0.91 (0.53)	0.99 (0.72)*	0.79 (0.51)	0.09
Arousal	0.811 (1.090)	0.854 (0.944)	0.730 (0.953)	0.781 (0.860)	0.540 (1.115)	0.023 (1.714)†	0.10
Positive mood	0.917 (0.757)	0.697 (0.666)	0.653 (0.799)	0.718 (0.634)	0.843 (0.775)*	0.576 (0.702)	0.14

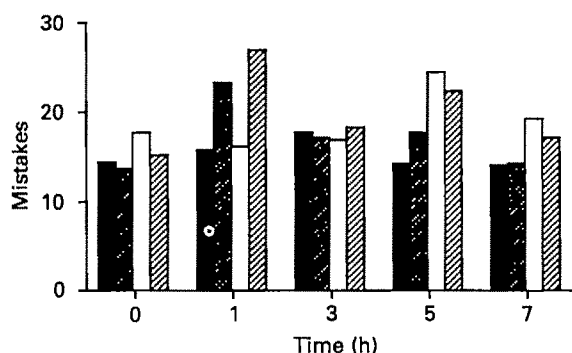


FIG. 1. Number of mistakes made on the eye-hand coordination task at 0, 1, 3, 5 and 7 h after injection of midazolam-fentanyl. Five and 7 h after injection of midazolam-fentanyl correspond with 1 and 3 h after ingestion of alcohol. ■ = Placebo injection, placebo beverage; ▒ = midazolam-fentanyl injection, placebo beverage; ▨ = placebo injection, alcohol beverage; ▩ = midazolam-fentanyl injection, alcohol beverage.

between injection of midazolam-fentanyl and subsequent ingestion of alcohol for eye-hand coordination (fig. 1); number of mistakes made in the test increased after both injection of midazolam-fentanyl and ingestion of alcohol, but the injection of i.v. drug did not potentiate the effects of alcohol.

DISCUSSION

We have demonstrated that short-acting sedatives used commonly in outpatient surgery impaired psychomotor performance and affected mood, but did not potentiate the effects of alcohol when this drug was ingested several hours after i.v. sedation. The acute impairment of performance by midazolam [18-21] and fentanyl [13, 22, 23] is consistent with other studies. Benzodiazepines have also been shown to increase sedation and confusion [19, 21, 24, 25]. There is some evidence that fentanyl may have effects on the CNS for several hours after administration [23]. However, impairment induced by drug in the present study, for the most part, did not last long and returned to baseline by 3 h after injection.

Alcohol had only modest effects in the present study. Interestingly, body sway, which is usually affected by this drug [26], was not affected. While large doses of alcohol appear to have impairing effects on a variety of measures of psychomotor performance [26], more inconsistent data are reported when small to moderate doses of alcohol are studied [10, 27, 28].

No interactions between midazolam-fentanyl

and alcohol were noted, although other studies have shown opposite results [5, 7–10]. However, differences in results between our study and those of other investigators may probably be accounted for by differences in interdrug interval: in other studies, benzodiazepines and alcohol were given together, whereas in our study the interval between i.v. sedation and ingestion of alcohol was set at 4 h. We attempted to use times and doses which mimicked the clinical situation. The results of the present study suggest that sedation with midazolam and fentanyl for outpatient surgery probably dissipates by the time the patient arrives home, and that effects from alcohol ingested at home will probably not be influenced by the recent use of midazolam and fentanyl.

REFERENCES

- Larkin H. Less money, more players in outpatient market. *Hospitals* 1989; 63: 26.
- Shannon K. Outpatient surgery up 77 percent: data. *Hospitals* 1985; 59: 54.
- Ogg TW. An assessment of postoperative outpatient cases. *British Medical Journal* 1972; 4: 573–576.
- Korttila K. Postanesthetic cognitive and psychomotor impairment. *International Anesthesiology Clinics* 1986; 24: 59–74.
- Linnoila M, Häkkinen S. Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. *Clinical Pharmacology and Therapeutics* 1974; 15: 368–373.
- Aranko K, Seppälä T, Pellinen J, Mattila MJ. Interaction of diazepam or lorazepam with alcohol. Psychomotor effects and bioassayed serum levels after single and repeated doses. *European Journal of Clinical Pharmacology* 1985; 28: 559–565.
- Hindmarch I, Subhan Z. The effects of midazolam in conjunction with alcohol on sleep, psychomotor performance and car driving ability. *International Journal of Clinical Pharmacology Research* 1983; 3: 323–329.
- Willumeit HP, Ott H, Neubert W, Hemmerling KG, Schratzer M, Fichte K. Alcohol interaction of lormetazepam, mepindolol sulphate and diazepam measured by performance on the driving simulator. *Pharmacopsychiatry* 1984; 17: 36–43.
- Morland J, Setekleiv J, Haffner JF, Stromsaether CE, Danielsen A, Wethe GH. Combined effects of diazepam and ethanol on mental and psychomotor functions. *Acta Pharmacologica et Toxicologica* 1974; 34: 5–15.
- Palva ES, Linnoila M, Saario I, Mattila MJ. Acute and subacute effects of diazepam on psychomotor skills: interaction with alcohol. *Acta Pharmacologica et Toxicologica* 1979; 45: 257–264.
- Linnoila M, Stapleton JM, Lister R, Moss H, Lane E, Granger A, Greenblatt DJ, Eckardt MJ. Effects of
- adinazolam and diazepam, alone and in combination with ethanol, on psychomotor and cognitive performance and on autonomic nervous system reactivity in healthy volunteers. *European Journal of Clinical Pharmacology* 1990; 38: 371–377.
- Hannington-Kiff JG. Measurement of recovery from outpatient general anaesthesia with simple ocular test. *British Medical Journal* 1970; 3: 132–135.
- Manner T, Kanto J, Salonen M. Simple devices in differentiating the effects of buprenorphine and fentanyl in healthy volunteers. *European Journal of Clinical Pharmacology* 1987; 31: 673–676.
- McNair DM, Lorr M, Droppleman LF. *Profile of Mood States (Manual)*. San Diego: Educational and Industrial Testing Service, 1971.
- de Wit H, Uhlenhuth EH, Hedeker D, McCracken SG, Johanson CE. Lack of preference for diazepam in anxious volunteers. *Archives of General Psychiatry* 1986; 43: 533–541.
- Little K, Penman E. Measuring subacute mood changes using the Profile of Mood States and visual analogue scales. *Psychopathology* 1989; 22: 42–49.
- Wilkinson L. *SYSTAT: The System for Statistics*. Evanston, IL: SYSTAT, Inc., 1986.
- Hindmarch I, Subhan Z. The effects of midazolam in conjunction with alcohol on sleep, psychomotor performance and car driving ability. *International Journal of Clinical Pharmacology Research* 1983; 3: 323–329.
- Gudgeon AC, Hindmarch I. Midazolam: Effects on psychomotor performance and subjective aspects of sleep and sedation in normal volunteers. *British Journal of Clinical Pharmacology* 1983; 16: 121S–126S.
- Schaffler K, Klausnitzer W. Acute effects of two dosages of orally administered midazolam on psychomotor performance in healthy volunteers. *Arzneimittel-Forschung* 1989; 39: 395–398.
- Nightingale JJ, Norman J. A comparison of midazolam and temazepam for premedication of day case patients. *Anaesthesia* 1988; 43: 111–113.
- Scamman FL, Ghoneim MM, Korttila K. Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiologica Scandinavica* 1984; 28: 63–67.
- Ghoneim MM, Mewaldt SP, Thatcher JW. The effect of diazepam and fentanyl on mental, psychomotor and electroencephalographic functions and their rate of recovery. *Psychopharmacology* 1975; 44: 61–66.
- Hargreaves J. Benzodiazepine premedication in minor day-case surgery: Comparison of oral midazolam and temazepam with placebo. *British Journal of Anaesthesia* 1988; 61: 611–616.
- Johanson CE, Uhlenhuth EH. Drug preference and mood in humans: diazepam. *Psychopharmacology* 1980; 71: 269–273.
- Linnoila M. Effects of drugs and alcohol on psychomotor skills related to driving. *Annals of Clinical Research* 1974; 6: 7–18.
- Fagan D, Tiplady B, Scott DB. Effects of ethanol on psychomotor performance. *British Journal of Anaesthesia* 1987; 59: 961–965.
- McManus IC, Ankier SI, Norfolk J, Phillips M, Priest RG. Effects on psychological performance of the benzodiazepine, loperazolam, alone and with alcohol. *British Journal of Clinical Pharmacology* 1983; 16: 291–300.

CLINICAL AND HAEMODYNAMIC EFFECTS OF MILRINONE IN THE TREATMENT OF LOW CARDIAC OUTPUT AFTER CARDIAC SURGERY

E. M. WRIGHT AND K. M. SHERRY

SUMMARY

We have studied the haemodynamic effects of i.v. milrinone, a new phosphodiesterase inhibitor, in patients with low cardiac output after cardiac surgery. Thirty-five patients with a cardiac index (CI) < 2.5 litre $\text{min}^{-1} \text{m}^{-2}$ and a pulmonary capillary wedge pressure (PCWP) > 8 mm Hg were given a loading dose of milrinone $50 \mu\text{g kg}^{-1}$ followed by an infusion at one of three rates: $0.375 \mu\text{g kg}^{-1} \text{min}^{-1}$, $0.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ or $0.75 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 12 h. After 1 h there were increases in CI (35%) ($P < 0.001$), heart rate (13%) ($P < 0.01$) and stroke volume index (19%) ($P < 0.005$). There were decreases in mean arterial pressure (12%) ($P < 0.01$), systemic vascular resistance (35%) ($P < 0.001$) and PCWP (24%) ($P < 0.05$). Pulmonary vascular resistance was unchanged or reduced and left ventricular stroke work index was unchanged or increased. The haemodynamic improvements were sustained throughout the infusion period. Milrinone was tolerated well: three patients developed tachycardia > 125 beat min^{-1} , one patient developed atrial fibrillation and one patient had a short run of atrial bigemini. We conclude that milrinone is a useful agent in the treatment of patients with a reduced cardiac output after cardiac surgery.

KEY WORDS

Heart: low cardiac output. Pharmacology: phosphodiesterase inhibitor, milrinone. Surgery: cardiac.

adrenergic agonists often in combination with direct acting peripheral vasodilators.

The bipyridine derivative, milrinone, is a new agent combining both inotropic and vasodilator effects. It is unrelated structurally to the catecholamines, the digitalis glycosides or the imidazolone derivative enoximone. It is a derivative of amrinone and has similar pharmacological and haemodynamic effects. It acts mainly via phosphodiesterase III inhibition, resulting in an increase in intracellular cyclic adenosine monophosphate (cAMP) [1]. Milrinone is 10 to 20 times more potent than amrinone and appears to be devoid of the important adverse effects of thrombocytopenia and abnormalities of liver function observed with the older drug [2, 3].

Previous studies have shown milrinone to have beneficial haemodynamic and clinical effects in patients with congestive cardiac failure [4-6] without increasing myocardial oxygen consumption [7]. We therefore performed a dose finding study to investigate the clinical and haemodynamic effects of i.v. milrinone at different infusion rates in a different group of patients, notably those with decreased cardiac output after cardiac surgery.

PATIENTS AND METHODS

Local Ethics Committee approval was obtained, and written informed consent from all patients. We studied adults having either valvular or coronary artery bypass surgery. All female patients were either post-menopausal or infertile. Patients were excluded if they had hepatic impairment, a plasma creatinine concentration $>$

A reduced cardiac output is a well recognized postoperative complication of cardiac surgery. It may be caused by either preoperative myocardial damage or perioperative myocardial ischaemia or infarction. Management may involve use of positive inotropic agents, traditionally beta-

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TABLE I. *Patient characteristics and operations*

	Group 1 (Milrinone 0.375 $\mu\text{g kg}^{-1} \text{min}^{-1}$)	Group 2 (Milrinone 0.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$)	Group 3 (Milrinone 0.75 $\mu\text{g kg}^{-1} \text{min}^{-1}$)
Sex (M:F)	8:2	8:7	7:3
Mean age (yr)	60.7 (46–76)	59.7 (51–76)	55.8 (43–68)
Mean weight (kg)	76.3 (56–87)	67.8 (50–84)	70.9 (51–92)
Operation (No.)			
Mitral valve replacement	2	5	3
Coronary artery bypass graft	7	7	6
Aortic valve replacement	1	2	1
Mitral and aortic valve replacement	0	1	0

250 $\mu\text{mol litre}^{-1}$ or a platelet count $< 100 \times 10^9 \text{ litre}^{-1}$. They were excluded also if they had significant arrhythmias or had received inotropic therapy 1 h before the study. Long acting vasodilators were withheld for 12 h before the infusion of milrinone.

A medical history, physical examination, ECG, chest x-ray and haematological analysis were made and serum concentrations of electrolytes measured 24 h before surgery. A suitably calibrated flow-directed, balloon-tipped pulmonary artery catheter was inserted before operation via the internal jugular vein and a radial artery cannulated for direct arterial pressure monitoring and blood-gas measurement. The anaesthetic method was not standardized. Extracorporeal circulation with non-pulsatile flow and moderate hypothermia were used during each operation. Myocardial protection was provided by cold cardioplegia solution and topical hypothermia.

After the operation, platelet count, ECG and chest x-ray were performed. The ECG was monitored continuously throughout the study. Haemodynamic assessment of the patients was undertaken 2 h after operation. The haemodynamic measurements performed were: cardiac output (CO) by thermodilution (an average of three values was taken), mean pulmonary artery wedge pressure (PCWP), systolic, diastolic and mean systemic arterial pressure (SAP), mean pulmonary arterial pressure (MPAP), mean right atrial pressure (RAP) and heart rate.

Derived haemodynamic values of cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), left ventricular stroke work index

(LVSWI), and right ventricular stroke work index (RVSWI) were calculated using standard formulae. The plasma potassium concentration was measured at 1-h intervals for 24 h after operation and maintained at 4–4.5 mmol litre^{-1} .

Patients were entered into the study if they had a stable CI $< 2.5 \text{ litre min}^{-1} \text{ m}^{-2}$ in the presence of a PCWP $> 8 \text{ mm Hg}$. A minimum of two sets of readings were taken at least 10 min apart. If the lesser of the two readings for either CI or PCWP was not within 15% of the greater reading, an additional reading was taken. If this value was not within 15% of the second reading, the patient was withdrawn from the study.

Accepted patients were given a loading dose of milrinone 50 $\mu\text{g kg}^{-1}$ over 10 min, followed by an infusion of 0.375 $\mu\text{g kg}^{-1} \text{min}^{-1}$ (first 10 patients), 0.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ (next 15 patients) or 0.75 $\mu\text{g kg}^{-1} \text{min}^{-1}$ (last 10 patients). The dose regimens were non-randomized.

The haemodynamic measurements were repeated at 15, 30 and 45 min, and 1, 3, 6 and 12 h after the start of milrinone. After 12 h the infusion was stopped and further haemodynamic measurements were taken after 2 and 4 h.

Statistical analysis

Analysis of variance was used to assess within- and between-group changes and Student's paired *t* test was used to test the significance of observed differences.

RESULTS

We studied 22 males and 13 females aged 43–76 yr. A summary of the patient data is given in table I. There was no significance difference

TABLE II. Mean (SD) haemodynamic data in groups 1 (milrinone $0.375 \mu\text{g kg}^{-1} \text{min}^{-1}$), 2 (milrinone $0.5 \mu\text{g kg}^{-1} \text{min}^{-1}$) and 3 ($0.75 \mu\text{g kg}^{-1} \text{min}^{-1}$). * $P < 0.05$; *** $P < 0.001$

		Time after infusion			
	Baseline	15 min	1 h	2 h	4 h
CI (litre min ⁻¹ m ⁻²)					
Group 1	1.95 (0.36)	2.99*** (0.6)	2.75*** (0.55)	2.84*** (0.44)	2.4* (0.4)
Group 2	1.93 (0.29)	2.51*** (0.42)	2.59*** (0.38)	2.82*** (0.43)	2.53* (0.58)
Group 3	2.06 (0.24)	2.52*** (0.47)	2.68*** (0.39)	2.87*** (0.58)	2.63* (0.88)
SVR (dyn s cm ⁻⁵)					
Group 1	1623 (312)	1000*** (242)	1063*** (254)	1030*** (253)	1393 (242)
Group 2	1811 (515)	1281*** (417)	1179*** (305)	1113*** (277)	1457 (544)
Group 3	1537 (359)	1160*** (286)	1091*** (281)	1023*** (285)	1426 (649)
HR (beat min ⁻¹)					
Group 1	79 (15.2)	91.8*** (19.3)	87.3* (16.3)	85.6* (11.2)	82 (11.0)
Group 2	84.8 (16.1)	97*** (20.2)	98.7*** (19.3)	98.5* (20.5)	89.7 (15.4)
Group 3	83 (16.1)	93.2* (18)	93.7* (19.3)	91 (21)	90.6 (15)
MAP (mm Hg)					
Group 1	79.4 (9.5)	73.6 (6.3)	71.4* (7.8)	73.2 (11.8)	84.8 (11)
Group 2	80 (12.6)	72.8* (15.5)	72*** (10)	72.4* (8.4)	83.7 (15.5)
Group 3	77.7 (12)	68.1* (10.3)	67.7*** (11.3)	70.1* (7.6)	80.3 (9.9)
PCWP (mm Hg)					
Group 1	10.7 (2.5)	8.8 (2.7)	9.1* (2.7)	9.4 (3.5)	12.5 (4.1)
Group 2	10.6 (2)	7.9*** (2.7)	8.1* (3.1)	9.0* (2.9)	12 (4.6)
Group 3	11.2 (4.2)	7.1*** (3.8)	7.4*** (3.2)	9.6 (5.3)	11.1 (6.5)
LVSWI (g mm ⁻²)					
Group 1	23.3 (5.1)	28.6* (4.8)	26.8 (5.3)	28* (5.4)	28.1* (3.9)
Group 2	21.8 (6)	23.5 (7.8)	23* (5.3)	25.8* (5.3)	27.3* (7.3)
Group 3	23.2 (8.9)	23.1 (8.8)	23.9 (7.1)	26.3 (8.9)	27.3 (10.9)
SVI (ml m ⁻²)					
Group 1	24.8 (3.6)	32.6* (4.5)	31.6* (4.6)	33.1* (3.5)	28.8* (2.3)
Group 2	23.1 (4.2)	26.4* (5.5)	26.8*** (5.5)	29.8*** (4.7)	28.2*** (5.1)
Group 3	25.4 (7.3)	27.5 (8.4)	28.8* (7.3)	32.1* (9.3)	29.4 (11.1)

between the baseline haemodynamic measurements in the three groups. Changes in haemodynamic variables are summarized in table II.

There was a significant ($P < 0.001$) improvement in CI in all three dose groups, which was

sustained throughout the period of infusion. The average increase was 34% after 15 min and 35% after 60 min. Between-groups analysis revealed a greater increase in CI in group 1 after 15 min ($P < 0.05$)—CI increased by 53%. This was the

only statistically significant difference between the groups.

SVR decreased significantly ($P < 0.001$) in the three groups, by an average 32% after 15 min and 35% after 1 h. The vasodilating effect of milrinone was sustained throughout the infusion and there was no significant difference between groups.

There was an initial increase in heart rate after the loading dose from an average of 82 beat min^{-1} to an average of 94 beat min^{-1} after 15 min and 93 beat min^{-1} after 1 h ($P < 0.01$). In three patients the increase in heart rate was considered a clinically adverse event. These patients are discussed further below.

Mean arterial pressure decreased and was significant ($P < 0.01$) in the mid and high dose groups after 15 min and in all groups after 1 h, when an average decrease of 9 mm Hg was seen. Although the decrease in arterial pressure was less in the low dose group, the difference between groups was not significant.

PCWP decreased by an average 26% after 15 min and was greater in the mid and high dose groups: 25% ($P < 0.001$) and 37% ($P < 0.001$), respectively. The differences between the three groups was not significant. SVI increased by an average of 18% after 15 min and 19% after 60 min ($P < 0.005$).

There was a significant decrease in MPAP in the mid and high dose groups after 15 min and a significant decrease in PVR in the low dose group after 15 min and 60 min. RAP was either unchanged or decreased and LVSWI was either unchanged or increased. There was no significant change in RVSWI.

Following discontinuation of the infusion, CI decreased by 11% and SVR increased by 35%. Heart rate and mean arterial pressure returned towards baseline values. Haematological and biochemical measurements before and after milrinone revealed no changes in platelet count or liver function.

Adverse events

Two patients developed sinus tachycardia. The first was a patient in the mid dose group who had an aortic valve replacement for aortic stenosis and whose heart rate increased from 87 to 127 beat min^{-1} after 6 h, settling to 86 beat min^{-1} 4 h after the infusion. The second was a patient in the high dose group who had coronary bypass surgery and showed a similar pattern of change in heart rate. A third patient who had a mitral valve replacement

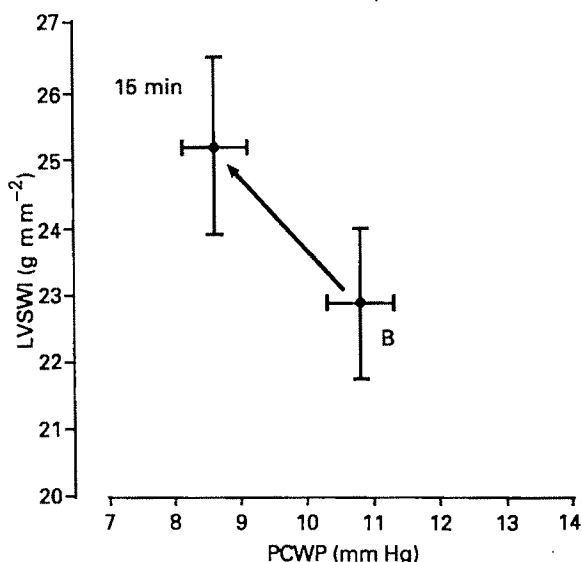


FIG. 1. Mean (SEM) LVSWI and PCWP of all patients at baseline (B) and 15 min after the start of the initial dose of milrinone.

for mitral regurgitation was in atrial fibrillation before receiving milrinone; heart rate increased from 105 to 135 beat min^{-1} within the first 1 h, but decreased after digoxin 0.625 mg. One patient in the high dose group who had a mitral valve replacement for mitral regurgitation had episodes of atrial fibrillation after commencing milrinone, reverting to sinus rhythm at the end of the infusion. One patient in the high dose group had a 15-s period of atrial bigemini.

DISCUSSION

The aim of our study was to investigate the effects of milrinone in a group of patients different from those studied previously. Thus the study design was open and non-comparative. Patients were not allocated randomly to the three dose groups; instead the dose of milrinone was increased sequentially because the sensitivity of patients to milrinone after cardiac surgery was not known.

The overall haemodynamic changes seen in our study confirmed the efficacy of milrinone as an inotrope and vasodilator. Although heart rate increased, there was also an increase in SVI, indicating that the improvement in CI was not caused solely by increase in heart rate. The improvement in left ventricular function after the initial loading dose of milrinone is shown in figure

1, which demonstrates an upward and leftward shift of left ventricular function, indicating that the changes were probably caused by a combination of reduced SVR and increasing myocardial contractility.

The vasodilating properties of milrinone were confirmed by the significant reduction in SVR seen in all three groups. This was accompanied by a decrease in MAP, but in no patients did this cause concern. The least value of MAP recorded was 52 mm Hg at 15 min in one patient in the middle dose group.

The only difference between the groups which was statistically significant was a greater increase in CI in group 1 at 15 min. It is interesting to note that PCWP was maintained better in this group at 15 min, although the difference was not statistically significant. As the decrease in SVR was similar in all three groups, it is possible that this reflects the infusion of greater volumes of fluid to the low dose group.

Our results otherwise showed no marked difference between the three dose groups. This probably reflects the fact that the initial loading dose of $50 \mu\text{g kg}^{-1}$ was the same for all three groups. Previous pharmacokinetic studies in patients with congestive cardiac failure have shown an elimination half-life of between 1.5 and 1.7 h [8, 9] after an i.v. dose of 12.5–75 $\mu\text{g kg}^{-1}$. Thus the initial blood concentration of milrinone would have been similar in all three groups. The haemodynamic improvement was sustained throughout the infusion period.

Discontinuation of milrinone was followed by a decrease in cardiac index, although not to baseline values, and probably reflects an underlying recovery. However, there was a marked increase in SVR, thus confirming that the vasodilatation was primarily caused by milrinone and was not merely a reflection of patient warming after cardiac bypass.

The incidence of adverse effects in this study was acceptable. We noted tachycardia as an important side effect in fewer than 10% of patients; however, this did not lead to clinical deterioration and it resolved on stopping the infusion. Anti-arrhythmic therapy was required for one patient who had chronic atrial fibrillation and suffered an increase in ventricular rate after milrinone was started; however, dose adjustment or drug discontinuation was not necessary. As arrhythmias are common in these patients, it is difficult to evaluate the arrhythmic effects of

milrinone. Electrophysiological studies have shown that i.v. milrinone enhances atrioventricular conduction, which may explain the increased ventricular rate in the patient with atrial fibrillation [10].

Long term trials of oral milrinone in chronic cardiac failure showed an increased mortality in patients assessed as New York Heart Association (NYHA) grade IV who received oral milrinone therapy, resulting in withdrawal of the oral preparation. However, trials of i.v. infusion of milrinone for 48 h to a similar group of patients with chronic cardiac failure (CCF) have shown a low incidence of adverse effects and no increased mortality [11].

An important question concerning the use of milrinone in postoperative cardiac surgical patients is its effect on myocardial oxygen consumption. The observed effects of milrinone produce opposing influences on the determinants of myocardial oxygen consumption: there is modest increase in heart rate and a modest decrease in systolic arterial pressure. In our study, the change in rate-pressure product was +7% after 60 min. There is evidence from previous studies that short-term administration of milrinone does not increase myocardial oxygen consumption [7, 12].

The combination of inotropic and vasodilator treatment in the management of patients with heart failure after cardiac surgery is often more beneficial than each therapy alone. Milrinone has been compared with dobutamine [5] and with sodium nitroprusside (SNP) [6] in studies of patients with CCF. When i.v. administration of milrinone and SNP were compared for a matched reduction in MAP or SVR, milrinone caused a significantly greater increase in LVSWI at the same or lesser left ventricular end-diastolic pressure (LVEDP). When compared with dobutamine, both milrinone and dobutamine improved cardiac index to a similar degree, but milrinone caused a significantly greater reduction in RAP, PCWP and LVEDP.

Milrinone has a mechanism of action which differs from that of the catecholamines. The latter increase cAMP by stimulation of myocardial beta-adrenergic receptors which are linked to the cAMP synthesizing enzyme adenylate cyclase. Prolonged use of catecholamines is known to lead to a loss of responsiveness caused first by down regulation of receptors and second because the prolonged increase in cAMP concentration leads

to increases in phosphodiesterase activity and enhances tolerance to beta-agonists. Large doses of catecholamines may also cause tachycardia and arrhythmias. Patients who require beta-adrenergic inotropic therapy for several days are therefore at risk of tachyphylaxis and the effects of prolonged catecholamine stimulation. Down regulation of beta receptors may occur also in patients with long-standing left ventricular failure. As phosphodiesterase inhibitors have a mechanism of action different from that of catecholamines, their efficacy is not reduced by down regulation of beta-receptors and thus they may be of benefit in patients requiring prolonged inotropic therapy and for patients with chronic left ventricular failure [13].

ACKNOWLEDGEMENT

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REFERENCES

1. Earl CQ, Linden JM, Weglicki WB. Inhibition of phosphodiesterase by amrinone and milrinone in rat heart. *Federation Proceedings* 1984; 43: 1942.
2. Massie B, Bourassa M, DiBianco R. Long term oral administration of amrinone for congestive heart failure: lack of efficacy in a multi-centre controlled trial. *Circulation* 1985; 71: 963-971.
3. Fitzpatrick PG, Cinquegrani MP, Vakiener AR, Baggs JG, Biddle TL, Liang CS. Hemodynamic and regional blood flow response to milrinone in patients with severe congestive heart failure: a dose-ranging study. *American Heart Journal* 1987; 114: 97-105.
4. Baim DS, McDowell AV, Cherniles J, Monrad ES, Parker JA, Edelson J, Braunwald E, Grossman W. Evaluation of a new bipyridine inotropic agent—milrinone—in patients with severe congestive heart failure. *New England Journal of Medicine* 1983; 309: 748-756.
5. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. *Circulation* 1986; 73 (Suppl. 3): 175-182.
6. Jasli BE, Fifer MA, Wright RF, Braunwald E, Colucci WS. Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure: Dose-response relationships and comparison to nitroprusside. *Journal of Clinical Investigation* 1985; 75: 645-649.
7. Monrad ES, Baim DS, Smith HS, Lanoue A, Braunwald E, Grossman W. Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure. *Circulation* 1985; 71: 972-979.
8. Wilson H, Larijani GE, Likoff M, Weber K, Rocci ML. The pharmacokinetics of milrinone in patients with chronic cardiac failure. *Clinical Pharmacology and Therapeutics* 1984; 35: 238 (Abstract No. A27).
9. Lesko LJ, McCue JE, Brady P, Alpert JS. Pharmacokinetics and pharmacodynamics of intravenous milrinone. *Circulation* 1984; 70 (Suppl. 2): 168 (Abstract No. 670).
10. Goldstein RA, Geraci SA, Gray EL, Rinkenberger RL, Hamilton Dougherty A, Naccarcelli GV. Electrophysiological effects of milrinone in patients with congestive heart failure. *American Journal of Cardiology* 1986; 57: 624-628.
11. Anderson JL, Baim DS, Fein SA, Goldstein RA, LeJemtel TH, Likoff MJ. Efficacy and safety of sustained (48 hour) intravenous infusions of milrinone in patients with severe congestive heart failure: a multicenter study. *Journal of the American College of Cardiology* 1987; 9: 711-722.
12. LeJemtel TH, Gumbardo D, Chadwick B, Rutman HI, Sonnenblick EH. Milrinone for long term therapy of heart failure: clinical experience with special reference to maximal exercise tolerance. *Circulation* 1986; 73 (Suppl. 3): 213-218.
13. Watson DM, Sherry KM, Weston GA. Milrinone a bridge to heart transplant. *Anaesthesia* 1991; 46: 285-287.

RENAL FUNCTION AFTER CARDIOPULMONARY BYPASS IN CHILDREN: COMPARISON OF DOPAMINE WITH DOBUTAMINE

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SUMMARY

We have compared low dose dopamine with dobutamine in conserving renal function in 142 children younger than 10 yr undergoing cardiopulmonary bypass (CPB). Patients were allocated randomly to receive a continuous infusion of either dopamine $2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ (group 1) or dobutamine $2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ (group 2) from the time of induction of anaesthesia. Administration of inotropes and diuretics was controlled strictly to agreed regimens. There was no clinical or statistically significant difference between the two groups in postoperative urine output, serum concentration of creatinine, fractional sodium excretion or need for diuretic therapy. This was true also of the subgroup of patients who received no other inotropic support. However, the subgroup of patients in group 1 who underwent periods of CPB in excess of 2 h ($n = 17$) had persistently greater postoperative serum concentrations of creatinine. Low dose dopamine did not appear to be superior to dobutamine for protection of renal function in these patients.

KEY WORDS

Kidney: function. Pharmacology: dobutamine, dopamine. Surgery: cardiopulmonary bypass, paediatric.

Acute renal failure has long been recognized as one of the more serious complications of cardiac surgery and cardiopulmonary bypass (CPB) in both adults [1] and children [2]. Dopamine has been used to improve and maintain renal function in several circumstances including the period of CPB in adults [3, 4]. This effect is thought to be a result of selective action on renal DA1 receptors [5, 6], enhancement of cyclic AMP activity [6] and suppression of aldosterone secretion [7]. It is

thought to increase renal blood flow [5, 8, 9], glomerular filtration rate (GFR) [8], sodium excretion [8] and urine output [10].

In adults, at equal systemic arterial pressure and flow, dopamine produces a greater diuresis and natriuresis than does dobutamine with similar GFR and effective renal plasma flow [3]. It also produces a greater reduction in renal vascular resistance and a greater increase in the renal blood flow:cardiac output ratio [4]. However, one small study of 14 children [11] was unable to demonstrate any benefit of low dose dopamine after CPB. Although both dobutamine and dopamine are useful inotropes after cardiac surgery [12, 13], there has been no study to determine their relative effect upon renal function in children.

We have compared the effects of continuous infusions of low dose dopamine and dobutamine on renal function in the perioperative period in children undergoing CPB.

PATIENTS AND METHODS

We studied 147 children aged 5 weeks to 9 yr undergoing elective open-heart surgery with cardiopulmonary bypass (CPB). Approval was obtained from the Ethics Committee of the Royal Liverpool Children's Hospital (Alder Hey) and informed signed consent was obtained from one or both parents of each child.

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TABLE I. Patient and cardiopulmonary bypass (CPB) characteristics (mean (SD) [range]). BSA = Body surface area

	Dopamine			Dobutamine		
	Whole group (n = 74)	Single inotrope (n = 37)	CPB > 2 h (n = 9)	Whole group (n = 68)	Single inotrope (n = 38)	CPB > 2 h (n = 8)
Age (months)	30 [1-108]	33 [4-94]	34 [2-77]	37 [1-117]	35 [1-103]	63 [13-117]
Sex (% male)	62	54	100	56	47	75
BSA (m ²)	0.49 (0.19) [0.2-0.9]	0.53 (0.24) [0.3-0.9]	0.51 (0.19) [0.3-0.8]	0.54 (0.21) [0.2-1.2]	0.53 (0.21) [0.2-1.0]	0.72 (0.26) [0.3-1.2]
CPB (min)	72 (41.8) [26-207]	45 (19.2) [26-120]	153 (31.8) [125-207]	77 (49.0) [25-265]	50 (19.1) [26-118]	177 (56.2) [131-265]
Cross-clamp (min)	37 (25.8) [0-159]	24 (14.0) [0-59]	55 (26.1) [35-159]	37 (29.5) [0-177]	24 (14.3) [0-62]	83 (52.6) [14-177]
Low flow (min)	5 (10.5) [0-40]	0.6 (3.0) [0-18]	19 (15.8) [0-36]	8 (16.4) [0-91]	2 (6.1) [0-13]	34 (34.7) [0-91]
Inotrope (No.)	1.7 (0.8) [1-4]	1.0	2.6 (0.7) [2-4]	1.7 (0.9) [1-4]	1.0	2.5 (0.8) [2-4]

Patients were allocated randomly to one of two groups using opaque sealed envelopes: group 1 received "low dose" dopamine ($2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$) and group 2 the same dose of dobutamine. The "trial" drug was started immediately after induction of anaesthesia and insertion of central venous cannulae and given continuously throughout CPB.

All patients received our standard premedication, induction and intraoperative management of CPB (Appendix).

If inotropic support was required before or after CPB, patients in group 1 received dobutamine as needed up to $10 \mu\text{g kg}^{-1} \text{min}^{-1}$; patients in group 2 received dopamine as needed up to $10 \mu\text{g kg}^{-1} \text{min}^{-1}$. If greater inotropic support was required, adrenaline was used in place of dobutamine or dopamine, respectively, maintaining a constant dose of the trial drug throughout. Isoprenaline or vasodilators (glyceryl trinitrate or epoprostenol) were used where indicated for bradycardia or afterload reduction.

Postoperative fluid therapy was managed as follows: a total fluid intake of 500 ml m^{-2} on the first day after operation, 750 ml m^{-2} on the second and 1000 ml m^{-2} on the third. Further diuretic therapy was given if urine output decreased to less than $2 \text{ ml kg}^{-1} \text{h}^{-1}$ (averaged over 2 h): mannitol 20% was given first at the rate of $1 \text{ ml kg}^{-1} \text{h}^{-1}$ for 5 h and if there was no response after 1 h, frusemide 1 mg kg^{-1} was given. The dose of frusemide was doubled every 30 min thereafter

until a urine output of $2 \text{ ml kg}^{-1} \text{h}^{-1}$ was obtained (up to a maximum dose of 4 mg kg^{-1}). Mannitol infusion was repeated at intervals of 12 h for the same criteria of urine output.

Blood and urine samples were obtained after induction of anaesthesia, before commencement of the trial drug, 30 min after cessation of CPB and thereafter at 6-h intervals for 48 h or until arterial and urinary catheters were removed, whichever occurred sooner. These samples were used to measure urine and serum concentrations of sodium and creatinine, blood-gas tensions and acid-base state. Fractional sodium excretion ($F_{\text{E}_{\text{Na}}}$) was calculated from the formula:

$$F_{\text{E}_{\text{Na}}} = 100 \times \text{Cu}_{\text{Na}} / \text{Cs}_{\text{Na}} \times \text{Cs}_{\text{Cr}} / \text{Cu}_{\text{Cr}}$$

where Cu and Cs are the urine and serum concentrations respectively of sodium (Na) or creatinine (Cr).

Data were analysed graphically to determine whether or not they were distributed normally. An unpaired Student's *t* test was used where data were found to be normally distributed. The Mann-Whitney *U* test was used for other data. Data are expressed as mean (SEM) except where stated otherwise.

RESULTS

Of the 147 children entered into the study, one child died in theatre and one soon after leaving theatre. The data on three patients were missing

TABLE II. Urine output and diuretic administration (mean (SD) [range])

	Dopamine			Dobutamine		
	Whole group (n = 74)	Single inotrope (n = 37)	CPB > 2 h (n = 9)	Whole group (n = 68)	Single inotrope (n = 38)	CPB > 2 h (n = 8)
Urine output (ml kg ⁻¹ h ⁻¹)	3.1 (1.1) [0-5.7]	3.1 (0.9) [1.8-5.7]	2.4 (1.1) [1.3-3.7]	3.3 (1.6) [0.1-9.5]	3.4 (1.3) [1.9-6.9]	2.3 (1.2) [0.1-4.4]
Total frusemide (µg kg ⁻¹ h ⁻¹)	99 (149) [0-1128]	47 (62) [0-300]	255 (350) [0-1128]	96 (89) [0-358]	65 (62) [0-166]	151 (109) [0-306]
Mannitol (g kg ⁻¹ /48 h)	0.9 (0.7) [0-3]	0.6 (0.5) [0-2]	1.3 (0.7) [0-2]	0.8 (0.8) [0-4]	0.5 (0.6) [0-2]	1.1 (1.1) [0-3]

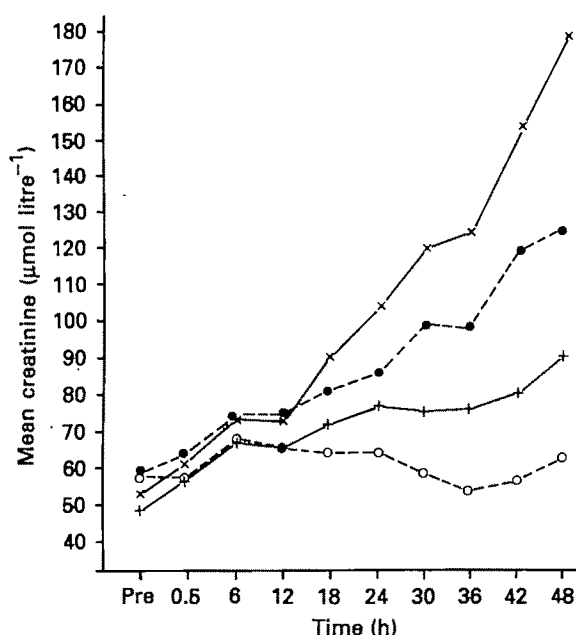


FIG. 1. Comparison of the mean serum concentrations of creatinine for four patient subgroups: low dose dopamine only (+); low dose dobutamine only (○); group 1 patients, CPB > 2 h (×); group 2 patients, CPB > 2 h (●).

or incomplete, leaving 142 cases (74 in group 1, 68 in group 2) for analysis.

The distribution of patients with regard to age, sex and body surface area is shown in table I, with CPB data and inotropic drug therapy.

There were no differences in renal function between the two groups as assessed by urine output, diuretic requirements (table II), serum concentration of creatinine and FE_{Na} . Five patients in each group required renal support (continuous arteriovenous haemofiltration or peritoneal di-

alysis); eight of these died (three in group 1; five in group 2).

More detailed analyses of the results to evaluate the effect of other variables (age (< 1 yr, 1-3 yr, > 3 yr), sex, bypass, aortic cross-clamp, low flow times and inotrope therapy) also showed no clinically or statistically significant differences. Assessment of the patients who received the trial drug in isolation and required no other inotropic agents (table II) also revealed no differences between groups.

Patients with prolonged CPB (> 2 h) ($n = 18$), aortic cross-clamp (> 1 h) ($n = 22$) or low flow times (> 20 min) ($n = 18$) showed greater impairment of renal function, but the numbers were too small to demonstrate any significant differences between the trial drugs (fig. 1).

DISCUSSION

We have been unable to show any advantage of low dose dopamine ($2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$) in comparison with a similar dose of dobutamine given without any other inotropic therapy. This would appear to be contrary to the findings in adults undergoing CPB [3, 4] or aortic cross-clamping [14], but accords with the findings of Girardin and colleagues [11]. A study in piglets [15] showed a more beneficial effect of dobutamine than dopamine on renal function. This may have been a result of a maturation process of dopamine receptors in the kidney [16]. However, we were unable to demonstrate any differences in our results throughout the age range of the patients in this study, and other workers have claimed that there is functional maturity of dopaminergic receptors, even in preterm infants [17].

These results question the value of an infusion

of low dose dopamine as a method of protecting renal function compared with dobutamine infused at the same rate.

Although the numbers of patients in the groups at greater risk of impaired postoperative renal function were too small to demonstrate statistically significant differences, there appeared to be a trend towards poorer renal function in the patients who received the low dose dopamine infusion. The reasons for this are not clear, because of the large number of variables in these patients, but the possibility remains that the patients who received the low dose dobutamine infusion benefited from the high dose of dopamine that they received for inotropic support or, conversely, that the larger doses of dobutamine received by the low-dose dopamine patients were more detrimental to renal function.

APPENDIX

MANAGEMENT OF CPB PATIENTS

Premedication. Trimeprazine 1.5 mg kg⁻¹ orally 3 h before operation; morphine 0.25 mg kg⁻¹ and atropine 20 µg kg⁻¹ i.m. 1 h before operation. Children younger than 6 months received atropine only; those between 6 months and 1 yr received atropine and morphine only.

Induction of anaesthesia. Thiopentone 4 mg kg⁻¹ with vecuronium 0.15 mg kg⁻¹.

Maintenance. Midazolam 120 µg kg⁻¹ h⁻¹ with diamorphine 12 µg kg⁻¹ h⁻¹.

Intraoperative fluids. Glucose 5% in 0.45% saline 1 ml kg⁻¹ h⁻¹, except for children weighing less than 10 kg who received 10% glucose in 0.45% saline at the same rate.

Before CPB all patients received potassium canrenoate 5 mg kg⁻¹. This dose was repeated at the end of CPB, together with frusemide 0.25 mg kg⁻¹.

Oxygenator. Either a bubble or a membrane oxygenator, the latter being used in the more complex cases.

Prime. A mixed blood and crystalloid prime was used to produce a final PCV of 0.25.

Cardioplegia. Blood cardioplegia was used for all cases.

Bypass. Full flow on CPB was calculated as either 100 ml kg⁻¹ min⁻¹ where body weight was less than 10 kg or 2.4 litre m⁻² min⁻¹ if greater than 10 kg.

None of the oxygenator fluid volume was re-infused after bypass.

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REFERENCES

1. Streisand JB, Wong KC. Anaesthesia for coronary bypass graft. *British Journal of Anaesthesia* 1988; 61: 97-104.
2. Chesney RW, Kaplan KB, Freedom RM, Haller JA, Drummond KN. Acute renal failure: An important complication of cardiac surgery in infants. *Journal of Pediatrics* 1975; 87: 381-388.
3. Hilberman M, Masada J, Stinson EB, Derby GC, Spencer RJ, Miller DC, Oyer PE, Myers BD. The diuretic properties of dopamine in patients after open-heart operation. *Anesthesiology* 1984; 61: 489-494.
4. Sato Y, Matsuzawa H, Eguchi S. Comparative study of effects of adrenaline, dobutamine and dopamine on systemic hemodynamics and renal blood flow in patients following open heart surgery. *Japanese Circulation Journal* 1982; 46: 1059-1072.
5. Kebabian JW, Calne DB. Multiple receptors for dopamine. *Nature (London)* 1979; 277: 93-96.
6. Insel PA, Snavely MD. Catecholamines and the kidney: Receptors and renal function. *Annual Review of Physiology* 1981; 43: 625-636.
7. North RH, McCallum RW, Contino C, Havelick J. Tonic dopaminergic suppression of plasma aldosterone. *Journal of Clinical Endocrinology and Metabolism* 1980; 51: 64-69.
8. Goldberg LI. Dopamine—clinical uses of an endogenous catecholamine. *New England Journal of Medicine* 1974; 291: 707-710.
9. Driscoll DJ, Gillette PC, Lewis RM, Hartley CJ, Schwartz A. Comparative hemodynamic effects of isoproterenol, dopamine and dobutamine in the newborn dog. *Pediatric Research* 1979; 13: 1006-1009.
10. Parker S, Carlon GC, Isaacs M, Howland WS, Kahn RC. Dopamine administration in oliguria and oliguric renal failure. *Critical Care Medicine* 1981; 9: 630-632.
11. Girardin E, Berner M, Rouge JC, Rivest RW, Friedli B, Paunier L. Effect of low dose dopamine on hemodynamic and renal function in children. *Pediatric Research* 1989; 26: 200-203.
12. Fiemeyer A, Karam J, Charron B, Lemardeley D. Dobutamine in cardiac surgery in babies. A retrospective study of 50 cases. *La Revue de Pédiatrie* 1985; 21: 176-186.
13. Lang P, Williams RG, Norwood WI, Castaneda AR. The hemodynamic effects of dopamine in infants after corrective cardiac surgery. *Journal of Pediatrics* 1980; 96: 630-634.
14. Salem MG, Crooke JW, McLoughlin GA, Middle JG, Taylor WH. The effect of dopamine on renal function during aortic cross clamping. *Annals of the Royal College of Surgeons of England* 1988; 70: 9-12.
15. Fiser DH, Fewell JE, Hill DE, Brown AL. Cardiovascular and renal effects of dopamine and dobutamine in healthy conscious piglets. *Critical Care Medicine* 1988; 16: 340-345.
16. Schwartz LB, Gewertz BL. The renal response to low dose dopamine. *Journal of Surgical Research* 1988; 45: 574-588.
17. Bhatt-Mehta V, Nahata MC. Dopamine and dobutamine in pediatric therapy. *Pharmacotherapy* 1989; 9: 303-314.

INFLUENCE OF HYPERTONIC VOLUME REPLACEMENT ON THE MICROCIRCULATION IN CARDIAC SURGERY

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SUMMARY

We have studied the effects of two types of volume replacement on the microcirculation in an open, controlled study in 45 patients undergoing aorto-coronary bypass grafting whose pulmonary capillary wedge pressure (PCWP) was < 5 mm Hg. Hypertonic saline prepared in hydroxyethylstarch solution (HS-HES, $n = 15$) and 6% HES 200/0.5 solution (6% HES; $n = 15$) were infused randomly before operation in order to double the PCWP. Patients not given an infusion served as controls ($n = 15$). Skin microcirculatory blood flow was investigated by laser Doppler flow (LDF) measured simultaneously at the forearm and forehead before and after cardiopulmonary bypass (CPB). Less HS-HES (3.8 (SD 0.3) ml kg^{-1}) than 6% HES-solution (9.7 (1.5) ml kg^{-1}) was necessary to double baseline PCWP. There were no differences in heart rate and mean arterial pressure (MAP) between the groups. Cardiac index (CI) increased significantly in both volume groups (HS-HES max. $+54\%$; 6% HES max. $+30\%$). Systemic vascular resistance (SVR) decreased after infusion of HS-HES (-30%) and after 6% HES (-19%) and remained almost unchanged in the control group. Plasma viscosity decreased after infusion of HS-HES and increased slightly in control patients ($+4\%$). In comparison with the 6% HES and particularly with the control group, LDF was significantly greater after infusion of HS-HES (forearm $+80\%$; forehead $+28\%$). LDF during CPB and thereafter was always greater than baseline values in the HS-HES group, whereas after bypass LDF was reduced in the 6% HES (-5%) and particularly in the control patients (-30%). No differences in temperature (oesophageal, rectal, forearm, forehead) occurred between groups. Changes in

MAP, CI, SVR, haemoglobin and viscosity did not correlate with skin blood flow. It was concluded that the preoperative infusion of HS-HES resulted in a significant improvement in microcirculation before, during and after CPB.

KEY WORDS

Blood: volume, microcirculation. Surgery: cardiovascular.

The "ideal" medium for intravascular volume replacement is still under discussion [1]; both crystalloid and colloid solutions have been advocated [2, 3]. Hypertonic solutions (HS) have been used in the treatment of refractory hypovolaemic shock ("small volume resuscitation") [4-9] and produced enhanced vasomotion and improved capillary flow [10]—effects which could not be achieved with conventional fluids.

Evaluation of the microcirculation is difficult. Laser Doppler flowmetry is a non-invasive technique by which changes in the skin microcirculation can be studied without risk to the patient [11-14]. A linear relationship with *in vitro* measurement of red cell flux and *in vivo* measurement of blood flow assessed by other methods has been demonstrated [13, 15]. The present study was designed to investigate the effect of volume therapy with a new hypertonic saline solution on microcirculation assessed by laser Doppler technique and to compare it with standard hydroxyethyl starch (HES) solution in cardiac surgery patients.

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PATIENTS AND METHODS

We studied 45 male patients undergoing elective aorto-coronary bypass grafting, in an open, controlled study which was approved by the hospital's Human Ethics Committee. All patients had a pulmonary capillary wedge pressure (PCWP) < 5 mm Hg after induction of anaesthesia. Patients with renal dysfunction, concomitant valvular disease, unstable angina or reduced left ventricular function (left ventricular ejection fraction (LVEF) $< 40\%$; left ventricular end-diastolic pressure (LVEDP) > 20 mm Hg) were excluded. The patients were allocated randomly to three groups:

HS-HES group ($n = 15$): A hypertonic saline solution prepared in low molecular weight (mol. wt) hydroxyethylstarch (HES) solution (6% HES: mol. wt 200 000 Da; molar substitution (MS) 0.5; NaCl 72 g litre⁻¹, HES 60 g litre⁻¹; osmolarity 2400 mosmol litre⁻¹ (Fresenius, Bad Homburg, FRG)) was infused before surgery in a volume sufficient to double baseline PCWP within 20 min.

HES group ($n = 15$): standard low mol. wt hydroxyethylstarch (HES) solution (6% HES: mol. wt 200 000 Da; MS 0.5; NaCl 9.0 g litre⁻¹; osmolarity 309 mosmol litre⁻¹ (Fresenius, Bad Homburg, FRG)) was given to the same endpoint as in the HS-HES group.

Control group ($n = 15$): no additional volume was infused.

Anaesthesia and cardiopulmonary bypass (CPB)

Premedication comprised flunitrazepam 0.025 mg kg⁻¹ i.m. and morphine 0.15 mg kg⁻¹ 1 h before anaesthesia, which was induced with midazolam 0.15 mg kg⁻¹ and fentanyl 4 µg kg⁻¹, followed by pancuronium 0.1 mg kg⁻¹. Anaesthesia was maintained with fentanyl (total dose 35 µg kg⁻¹), midazolam (total dose 0.60 mg kg⁻¹), and pancuronium (total dose 0.25 mg kg⁻¹). The patient's lungs were ventilated with an FiO_2 of 1.0 and zero end-expiratory pressure (ZEEP) until the end of the operation. The two groups did not differ in ventilation patterns or anaesthetic technique.

CPB was performed using membrane oxygenators (Sorin 41, Sorin, Torino, Italy). A flow of 2.4 litre min⁻¹ m² was used throughout, and slight hypothermia (lowest rectal temperature 33.2 (0.7) °C) was maintained. The circuit was

primed with Ringer's solution 1000 ml, 5% glucose 1000 ml and 5% human albumin 250 ml. Bretschneider's cardioplegic solution 1000 ml (Na⁺ 15 mmol litre⁻¹, no Ca²⁺, mannitol 20 mmol litre⁻¹, buffered with histidine 180 mmol litre⁻¹) was used to preserve myocardial function. During and after weaning from CPB, haemoconcentration was performed with a haemofiltration system (HF-80, Fresenius, Bad Homburg, FRG). Ringer's solution was added to the heart-lung machine as required to maintain flow; when the haemoglobin concentration was < 7 g dl⁻¹, packed red cells were added to the perfusate. Blood remaining in the extracorporeal oxygenation equipment was salvaged by haemofiltration and retransfused until the end of the operation. After CPB, protamine was given to antagonize the heparin.

Heart rate (HR), mean arterial pressure (MAP), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP) and cardiac output (CO) (thermodilution technique) were measured. Derived parameters (cardiac index (CI); systemic vascular resistance (SVR)) were calculated from standard formulae.

Changes in microvascular blood flow were measured with a two-channel laser Doppler skin blood flux monitor (MBF-3D, Moor Instruments, Devon). This uses a low power, near infra-red laser diode as a light source, optical fibres to transmit light and photodiode detection of the collected light. The laser Doppler measures blood flow in approximately 2 mm³ of tissue. The device yields electrical signals proportional to the number of moving blood cells and the average velocity of the red blood cells (RBC). The reflected light is registered by a photodetector and processed in real time to yield an output (mV) of arbitrary flow units. The product of the volume and the velocity of the RBC is the RBC flux or laser Doppler flow (LDF), which reflects local microvascular blood flow [16]. In addition, the concentration of RBC (number/unit volume) (= concentration) and the mean RBC speed (= speed) in the local tissue region were recorded. Details of technique and theoretical background have been described elsewhere [17]. One laser probe was placed on the patient's forehead (probe 1), and the other on the inner part of the right forearm (probe 2). Cutaneous temperature probes were placed next to the laser Doppler probes to measure skin temperatures simultaneously.

TABLE I. Patient data, preoperative heart catheterization variables, and data from cardiopulmonary bypass (CPB) (mean (range or SD)). LVEF = Left ventricular ejection fraction; LVEDP = left ventricular end-diastolic pressure; Ischaemia = duration of aortic cross-clamping; Infusion = Ringer's solution infused until first day after op. Significant differences ($P < 0.05$): * compared with control group; † compared with HES group

	HS-HES	HES	Control
Age (yr)	61.3 (55-65)	60.6 (54-67)	58.6 (54-62)
Weight (kg)	71.6 (7.7)	77.7 (5.5)	75.0 (6.6)
LVEF (%)	67.1 (4.4)	70.3 (5.6)	70.1 (5.4)
LVEDP (mm Hg)	14.9 (4.4)	12.2 (3.5)	11.2 (2.7)
CPB (min)	69.3 (15.1)	73.4 (13.1)	70.6 (16.9)
Ischaemia (min)	41.7 (9.4)	45.5 (8.9)	41.3 (6.9)
Fluid balance during CPB (ml)	-450 (200)*†	+200 (200)	+600 (200)
Infusion (ml)	1660 (300)*	1900 (400)*	2400 (400)

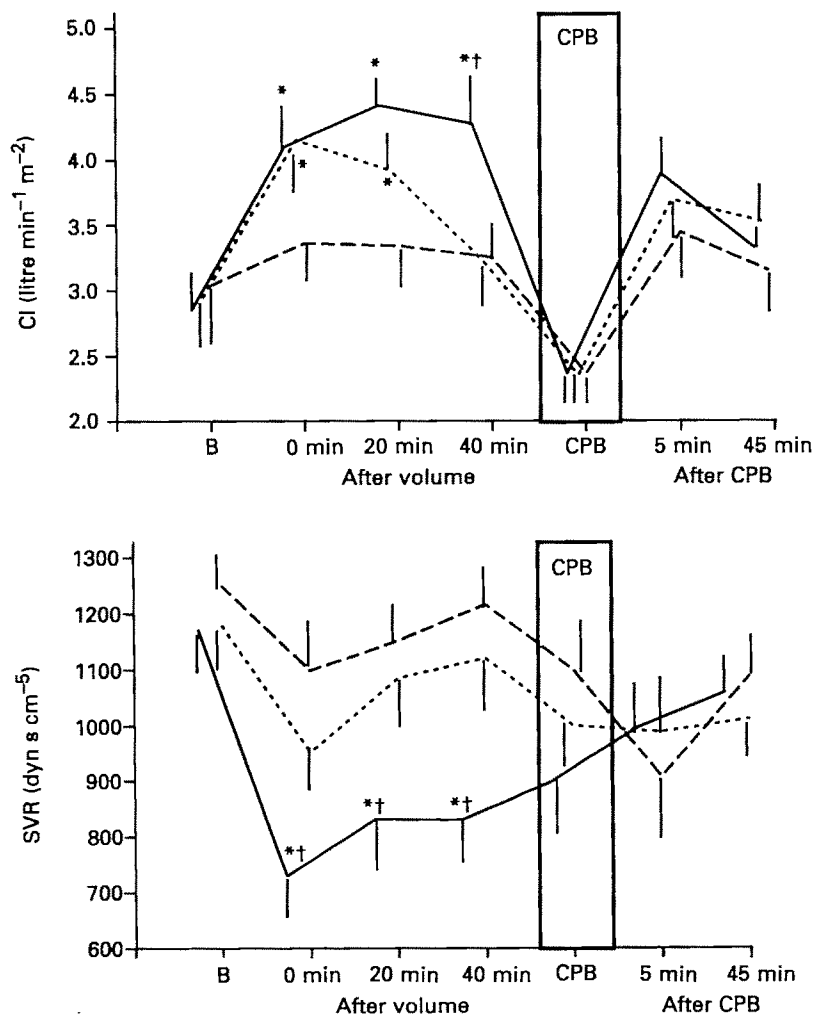


FIG. 1. Changes in cardiac index (CI) and systemic vascular resistance (SVR) in the three groups. CPB = Cardiopulmonary bypass. Significant differences ($P < 0.05$): * compared with control group; † compared with HES group.

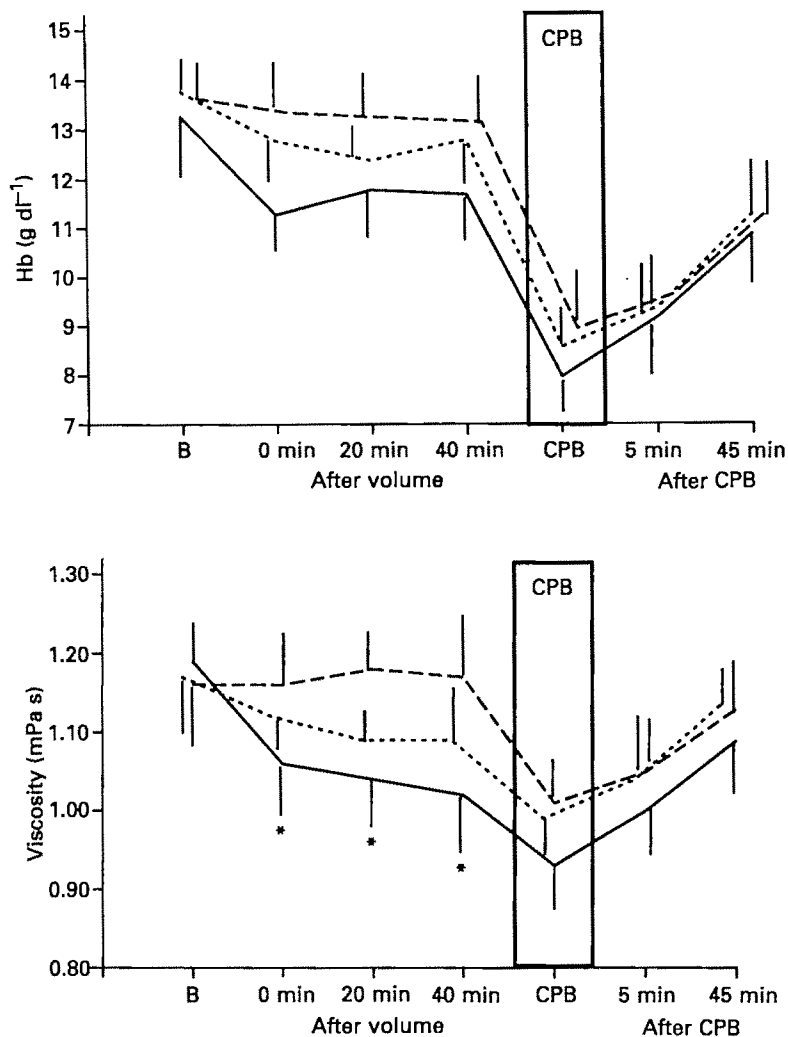


FIG. 2. Changes in haemoglobin (Hb) and plasma viscosity. CPB = Cardiopulmonary bypass.

* $P < 0.05$ compared with control group.

Haemoglobin (Hb), PCV, colloid osmotic pressure (COP) (sartorius membrane 20 000 Da), and plasma viscosity were measured from arterial blood samples. Measurements were performed after induction of anaesthesia when cardiovascular stability was attained (baseline values), immediately and 20 and 40 min after the end of the volume infusion, 20 min after the start of CPB, 5 min after weaning from CPB, and at the end of the operation.

Statistical analysis

Results were expressed as mean (SD). Data were analysed using one-way (biometric data, data

from perioperative period) and two-way analyses of variance (all haemodynamic variables), including multi-variate analysis of variance followed by Scheffé's test. Alterations in microcirculation from baseline values are presented as percentage changes because the output of the laser Doppler flow monitor is in arbitrary flow units. These percentage changes were additionally tested by *H* test (Kruskal-Wallis). Analysis of covariance and regression analysis were used to detect a relationship between two variables. $P < 0.05$ was considered statistically significant.

TABLE II. Mean (SD) changes from baseline (%) in skin blood flow measured at the forehead and forearm. CPB = Cardiopulmonary bypass; LDF = laser Doppler flow. Significant differences ($P < 0.05$): * compared with control group; † compared with HES group

LDF	After volume infusion			During CPB	After CPB	
	0 min	20 min	40 min		5 min	45 min
Forehead						
HS-HES	+29 (10)*†	+30 (11)*†	+20 (9)*†	+10 (10)*†	+21 (12)*†	+9 (7)*†
HES	-8 (8)	+4 (8)*	+3 (6)*	-15 (9)*	-2 (9)*	-4 (7)*
Control	-12 (6)	-22 (11)	-21 (10)	-30 (10)	-22 (11)	-31 (12)
Forearm						
HS-HES	+41 (14)*†	+89 (15)*†	+78 (15)*†	+51 (12)*†	+57 (15)*†	+40 (12)*†
HES	+7 (5)	+57 (16)*	+41 (17)*	+23 (17)	+25 (15)	+14 (11)
Control	+6 (5)	+1 (10)	+8 (15)	+29 (13)	+30 (13)	+10 (10)

TABLE III. Mean (SD) changes from baseline (%) in concentration measured at the forehead and forearm. CPB = Cardiopulmonary bypass. Significant differences ($P < 0.05$): * compared with control group; † compared with HES group

Concn	After volume infusion			During CPB	After CPB	
	0 min	20 min	40 min		5 min	45 min
Forehead						
HS-HES	+21 (11)*	+20 (12)*	+10 (10)	-15 (11)	-9 (9)*	-1 (8)*
HES	+9 (9)*	+2 (8)	+5 (9)	-25 (17)	-18 (11)	-10 (10)
Control	-9 (12)	-10 (12)	-13 (11)	-24 (16)	-24 (13)	-23 (13)
Forearm						
HS-HES	+30 (10)*†	+65 (18)*†	+32 (13)	+18 (13)	+20 (18)	+35 (15)*†
HES	+12 (10)	+21 (15)	+26 (16)	+10 (13)	+5 (12)	+6 (8)
Control	+12 (9)	+11 (16)	+17 (12)	+13 (12)	+21 (13)	+7 (10)

RESULTS

The three groups did not differ in patient characteristics, anaesthesia and CPB procedure (table I).

Significantly less HS-HES (3.8 (0.3) ml kg⁻¹) than 6% HES solution (9.7 (1.5) ml kg⁻¹) was required to double baseline PCWP. PCWP remained increased in the HS-HES patients until the onset of CPB. Fluid balance during CPB was significantly different between groups: HS-HES patients showed a negative balance (-450 (200) ml), while HES patients (+200 (200) ml) and the control group (+600 (200) ml) had a positive fluid balance. Moreover, control patients received significantly more Ringer's solution until the morning of the first day after operation (table I).

There was no difference in HR, MAP or PAP between groups throughout the study. CI (fig. 1) increased in both volume groups (HS-HES max. +54%; 6% HES max. +30%), but only remained increased 40 min after the infusion in the

HS-HES patients. SVR decreased after infusion of HS-HES (-30%) and after HES (-19%), but remained almost unchanged in the control group (table I).

Hb decreased in all patients in whom volume was infused, but there was no difference between the two groups (fig. 2). Plasma viscosity decreased significantly after infusion of HS-HES (-16%); HES-patients had a less pronounced decrease (-6%), and viscosity in the control group increased slightly (+4%) (fig. 2).

LDF increased significantly in the HS-HES patients when measured both at the forearm (max. +80%) and at the forehead (max. +28%) (table II). LDF measured at the forearm was also increased significantly in the HES-patients (+42%), but remained almost unchanged in control patients. During CPB and thereafter, LDF in the HS-HES patients was always greater than baseline values, whereas after bypass LDF measured at the forehead was reduced in HES (-5%) and, particularly, in control patients (-30%). Speed measured at the forehead was

TABLE IV. Mean (SD) changes from baseline (%) in speed measured at the forehead and forearm. CPB = Cardiopulmonary bypass. Significant differences ($P < 0.05$): *compared with control group; †compared with HES group

Speed	After volume infusion			During CPB	After CPB	
	0 min	20 min	40 min		5 min	45 min
Forehead						
HS-HES	+10 (9)	+9 (9)	+11 (9)	+33 (14)*	+30 (12)*	+4 (5)
HES	+7 (8)	+8 (6)	+2 (4)	+20 (15)	+19 (16)	+6 (4)
Control	+2 (8)	-1 (6)	-5 (9)	+9 (17)	+11 (12)	+11 (9)
Forearm						
HS-HES	+21 (16)	+31 (13)*	+58 (16)*†	+67 (19)*†	+36 (12)*	+12 (10)
HES	+10 (10)	+28 (14)*	+28 (14)*	+30 (14)*	+28 (14)	+25 (17)
Control	-1 (9)	-2 (10)	-11 (14)	+12 (12)	+10 (13)	+5 (16)

almost unchanged after volume infusion, but was significantly greater in the HS-HES patients at the end of CPB (table III). In the forearm, speed was most increased in the HS-HES patients, whereas it remained unchanged in the controls. Concentrations were always greatest in those patients who received HS-HES (table IV).

There were no differences in temperature (oesophageal, rectal, forearm, forehead) among the groups.

Changes in MAP, CI, SVR, Hb and viscosity did not correlate with LDF flow, speed or concentration (regression analysis and analysis of covariance).

DISCUSSION

The microcirculation represents the common path of the respiratory and circulatory systems. In conditions such as shock, ischaemia and cardiopulmonary bypass (CPB), microcirculatory flow is altered significantly, often becoming inadequate to fulfil the nutritive role of the circulation [18]. This insufficiency can occur with a normal circulation, but it is aggravated significantly when cellular dysfunction increases the hydraulic resistance of the capillaries [18].

During CPB, red and white blood cells are damaged, so that their ability to flow through the capillaries is reduced because of impaired deformability [19-21]. Al-Khaja and colleagues [20] found that CPB was associated with significant disturbances of blood cell rheology and reduced microcirculatory flow. The combination of blood trauma, alterations in plasma factors and impaired blood cell rheology are thought to be associated with postoperative complications or mortality after cardiac surgery [20, 22]. Mazzoni and co-

workers [23] demonstrated that, during reduced perfusion induced by haemorrhagic hypotension, the endothelium of the capillaries was swollen and lost its capacity for regulating its volume, thus affecting their hydraulic conductivity.

During CPB, microcirculatory dysfunction is caused by both reduced arteriolar pressure and endothelial swelling, induced by the perfusion process. Blood contact with foreign surfaces of the extracorporeal oxygenation equipment and damage to the cells by the roller pumps induce activation of several mediator cascades, the end products of which may affect the microcirculation by vasoconstriction [24]. Swelling of the capillary endothelium may be caused by increased permeability (capillary leakage) also induced by the activated mediators. Moreover, poorly perfused capillaries themselves may release and activate mediators promoting cellular adhesion and vasoconstriction, instituting a cycle of progressive tissue damage by deterioration in the microcirculation [18].

Hypertonic volume replacement may correct this dysfunction by increasing perfusion pressure, improving capillary flow distribution, reducing endothelial swelling and haemodilution [18, 23]. This supposition has been confirmed in animals, where 7.5% saline solution improved organ function in experimental shock [3]. The results of the present study showed improved microcirculatory function in patients given the hypertonic solution in comparison with those given isotonic solutions.

The beneficial effects of crystalloid hypertonic solutions are reported to be transient [25]. The addition of a synthetic colloid (dextran) significantly prolonged the effect [9, 26]. The mixture of hypertonic saline solution and HES used in the

present study may have less effect on coagulation and less risk of inducing anaphylactic reactions [27] than mixtures with dextran and it has been used safely in other studies [28].

CPB periods in our study were moderate (less than 90 min) and changes in microcirculation were not expected to be severe. However, as demonstrated by Mazzoni and colleagues [23], the more swollen the endothelium the greater the effect of hypertonic solution in improving capillary flow. Thus the beneficial effects of pre-operative infusion of HS-HES might be more evident in longer procedures, which are associated with an increasing risk of deteriorating capillary integrity and microcirculatory perfusion [29].

It has been suggested that changes in cutaneous blood flux might be a sensitive indicator of alterations in MAP and cardiac output [30], but this was not confirmed by our studies. There was no correlation in this study between cardiovascular and laboratory variables and those measured by LDF.

It was concluded that infusion of hypertonic HS-HES solution resulted in a significant increase in microcirculatory skin blood flow. The improved blood flux during and after CPB might be beneficial, particularly in prolonged procedures.

REFERENCES

1. Prough DS, Johnston WE. Fluid restoration in septic shock: no solution yet. *Anesthesia and Analgesia* 1989; 69: 699-704.
2. London ML. Plasma expansion in cardiovascular surgery: practical realities, theoretical concerns. *Journal of Cardiothoracic Surgery* 1988; 6 (Suppl. 1): 39-49.
3. Karanko MS, Klossner JA, Laaksonen VO. Restoration of volume by crystalloids versus colloid after coronary artery bypass: hemodynamics, lung water, oxygenation, and outcome. *Critical Care Medicine* 1987; 15: 559-566.
4. Armistead CWJ, Vincent JL, Preiser JC, De Backer D, Thuc Le M. Hypertonic saline solution-hetastarch for fluid resuscitation in experimental septic shock. *Anesthesia and Analgesia* 1989; 69: 714-720.
5. Holcroft JW, Vassar MJ, Turner JE, Derlet RW, Kramer GC. 3% NaCl and 7.5% NaCl/dextran 70 in the resuscitation of severely injured patients. *Annals of Surgery* 1987; 206: 279-288.
6. DeFilippe J, Timoner J, Velasco IT, Lopes OU, Rocha-E-Silva M. Treatment of refractory hypovolaemic shock by 7.5% sodium chloride injections. *Lancet* 1980; 2: 1002-1004.
7. Kramer GC, Perron PR, Lindsey DC, Ho HS, Gunther RA, Boyle WA, Holcroft JW. Small-volume resuscitation with hypertonic saline dextran solution. *Surgery* 1986; 100: 239-247.
8. Kreimeier U, Messmer K. New perspectives in resuscitation and prevention of multiple organ system failure. In: Baethmann A, Messmer K, eds. *Surgical Research: Recent Concepts and Results*. Berlin, Heidelberg: Springer, 1987; 39-50.
9. Maningas PA, DeGuzman LR, Tillman FJ, Hinson CS, Priegnitz KJ, Volk KA, Bellamy RF. Small-volume infusion of 7.5% NaCl in 6% Dextran 70 for the treatment of severe hemorrhagic shock in swine. *Annals of Emergency Medicine* 1986; 15: 1131-1137.
10. Read RC, Johnson JA, Vick JA. Vascular effects of hypertonic solutions. *Circulation Research* 1960; VIII: 538-544.
11. Holloway GAJ, Watkins DW. Laser Doppler measurement of cutaneous blood flow. *Journal of Investigation Dermatology* 1977; 69: 306-309.
12. Powers BW, Frayer WW. Laser Doppler measurement of blood flow in the microcirculation. *Plastic and Reconstructive Surgery* 1978; 61: 250-255.
13. Nilsson GE. Signal processor for laser Doppler tissue flowmeters. *Medical and Biological Engineering and Computing* 1984; 22: 343-348.
14. Micheels J, Alsbjorn B, Sorensen B. Laser doppler flowmetry. A new non-invasive measurement of microcirculation in intensive care? *Resuscitation* 1984; 12: 31-39.
15. Nitzan M. Simultaneous measurement of skin blood flow by the transient thermal-clearance method and laser Doppler flowmetry. *Medical and Biological Engineering and Computing* 1988; 26: 407-410.
16. Song CW, Chelstrom LM, Levitt SH, Haumschild DJ. Effects of temperature on blood circulation measured with the laser Doppler method. *International Journal of Radiation and Oncology Biological Physics* 1989; 17: 1041-1047.
17. Boggett D, Blond J, Rolfe P. Laser doppler measurements of blood flow in skin tissue. *Journal of Biomedical Engineering* 1985; 7: 225-232.
18. Intaglietta M. Objectives for the treatment of the microcirculation in ischemia, shock, and reperfusion. In: Vincent JL, ed. *Update in Intensive Care and Emergency Medicine*. Berlin, Heidelberg, New York: Springer, 1989; 293-298.
19. Hirayama T, Vamaguchi H, Allers M, Roberts D, William-Olsson G. Changes in red cell deformability associated with anaesthesia and cardiopulmonary bypass in open-heart surgery. *Scandinavian Journal of Thoracic and Cardiovascular Surgery* 1985; 19: 257-262.
20. Al-Khaja N, Belboul A, Bergman P, Roberts D, William-Olsson G. Cutaneous microcirculation and blood rheology following cardiopulmonary bypass. Laser Doppler flowmetric and blood cell rheologic studies. *Scandinavian Journal of Thoracic and Cardiovascular Surgery* 1988; 22: 149-153.
21. Ekstroem S, Koul BL, Sonnenfeld T. Decreased red cell deformability following open-heart surgery. *Scandinavian Journal of Thoracic and Cardiovascular Surgery* 1983; 17: 41-44.
22. Roberts D, Dernevik L, Hirayama T. Reduced peri- and post-operative mortality following the use of urea during elective cardiopulmonary bypass. A proposed treatment for the prevention of reduced red cell deformability during open heart surgery. *Scandinavian Journal of Thoracic and Cardiovascular Surgery* 1987; 38: 75-80.
23. Mazzoni MC, Borgström P, Arfors KE, Intaglietta M.

- Dynamic fluid redistribution in hyperosmotic resuscitation of hypovolemic hemorrhage. *American Journal of Physiology* 1988; **255**: H629-H637.
24. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW. Complement activation during cardiopulmonary bypass. Evidence for generation of C3a and C5a anaphylatoxins. *New England Journal of Medicine* 1981; **304**: 497-503.
25. Smith GJ, Kramer GC, Perron P, Nakayama SI, Gunther RA, Holcroft JW. A comparison of several hypertonic solutions for resuscitation of bled sheep. *Surgical Research* 1985; **39**: 517-528.
26. Nakayama SI, Sibley L, Gunther RA, Holcroft JW, Kramer GC. Small-volume resuscitation with hypertonic saline (2.400 mOsm/litre) during hemorrhagic shock. *Circulatory Shock* 1984; **13**: 149-159.
27. Strauss RG. Volume replacement and coagulation: a comparative review. *Journal of Cardiothoracic Anesthesia* 1988; **2** (Suppl. 1): 24-32.
28. Boldt J, Kling D, Herold C, Dapper F, Hempelmann G. Volume therapy with hypertonic hydroxyethyl starch solution in cardiac surgery. *Anaesthesia* 1990; **45**: 928-934.
29. Wesselink P, Feola M, Alfrey CP, Suzuki M, Ross JL, Kennedy JH. Prolonged partial cardiopulmonary bypass and the integrity of small blood vessels. *Journal of Thoracic and Cardiovascular Surgery* 1970; **60**: 789-794.
30. Waxmann K, Formosa P, Soliman H, Tominaga G, Police A, Hyatt J. Laser Doppler velocimetry in critically ill patients. *Critical Care Medicine* 1987; **8**: 780-783.

RELATIONSHIP BETWEEN ANALGESIA AND RESPIRATORY DEPRESSION FOR MU OPIOID RECEPTOR AGONISTS IN MICE

D. G. STOTT AND B. J. PLEUVRY

SUMMARY

The relationship between analgesic activity, measured as the hot plate reaction time, and respiratory depression, measured as ventilatory frequency, was investigated in mice for a variety of mu opioid receptor agonists with differing selectivities for mu receptors compared with delta receptors. There was a weak correlation between analgesia and respiratory depression for opioids with the greatest selectivity for mu opioid receptors compared with delta receptors, such as alfentanil. The strength of the correlation increased for opioids which had greater delta receptor activity, such as morphine and fentanyl. Etorphine, which has almost equal affinity for mu, delta and, incidentally, kappa receptors, showed a strong correlation between analgesia and respiratory depression. We conclude that the predictability of the degree of respiratory depression produced by a given analgesic dose of an opioid appears to decrease with its selectivity for mu opioid receptors, at least in the mouse.

KEY WORDS

Analgesics: opioid, mu agonists. Complications: respiratory depression.

For many years, standard textbooks have reiterated the observation that, for a given analgesic effect, most opioids produced the same degree of respiratory depression as seen with morphine [1]. The possibility that this need not always be the case emerged from the work of McGilliard and Takemori, who suggested that opioid analgesia and respiratory depression might be mediated by different opioid receptors [2]. Although their evidence, using naloxone antagonism, aroused considerable discussion as to the relevance of pA_2 values *in vivo* (pA_2 being a measure of antagonism normally applied to the *in vitro* situation), it

prompted others to continue this line of investigation. Using selective irreversible mu receptor antagonists, two groups of workers [3, 4] were able to demonstrate that respiratory depression was not antagonized by mu receptor block in the unstressed rodent. One of the compounds used was naloxonazine, which Pasternak's group had reported was selective for a high affinity subgroup of mu receptors designated mu 1. Thus Ling and colleagues [3] concluded that mu 1 receptors were not involved with respiratory depression. Other workers have been unable to demonstrate mu isoreceptors with selectivity for analgesia [5]. The situation is complicated further by the fact that Ward and Takemori [4] noted that an irreversible mu antagonist could antagonize opioid respiratory depression if more stressful methods of assessing ventilation were used. The possibility that delta receptors are involved in opioid-induced respiratory depression has arisen from the observation that delta receptor antagonists may antagonize fentanyl-induced respiratory depression, but not analgesia, in the dog [6].

In the present study, the relationship between analgesia and respiratory depression has been investigated in a series of opioids with significant affinity for mu opioid receptors, but with differing selectivities for mu compared with delta receptors, ranging from alfentanil (602 (SEM 52)) and sufentanil (24.9 (1.9)) [7] to etorphine which has similar affinity for mu, delta and kappa receptors [8]. Relatively stress free measures of analgesia (or antinociceptive activity) and respiratory depres-

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TABLE I. *Time intervals between consecutive readings of ventilatory frequency and hot plate reaction times, and drug doses used*

	Fentanyl	Sufentanil	Alfentanil	Morphine	Etorphine
Interval (min)	4	15	2	15	10
Doses	(mg kg ⁻¹)	(µg kg ⁻¹)	(mg kg ⁻¹)	(mg kg ⁻¹)	(µg kg ⁻¹)
	0.025	10.0	0.125	2.5	2.0
	0.05	20.0	0.25	5.0	4.0
	0.1	40.0	0.5	10.0	5.0
	0.2		0.6		8.0
	0.4		0.8		10.0
					15.0

sion have been used in mice to reduce the influence of stress on the results obtained.

MATERIALS AND METHODS

MF1 mice weighing 25–30 g were used in the study, which was approved by the Home Office under the Animals (Scientific Procedures) Act 1986 (licence number 50/00499). Each group consisted of 12 MF1 male mice, which received an i.p. injection of an opioid (fentanyl, alfentanil, sufentanil, morphine or etorphine) on an mg kg⁻¹ basis in a dose volume of not more than 0.1 ml per 10 g body weight. Control values of ventilatory frequency and hot plate reaction times were recorded before any injections were given. The subsequent time intervals between the recordings, and the doses of each drug are given in table I. Each group of 12, concurrently tested, mice were allocated randomly to saline controls or one of the several doses of an individual opioid. Thus only one or two mice in the group might receive a particular dose of drug. Experiments were repeated until group sizes of 12 were obtained for each dose of drug. A saline time-matched control was available, therefore, for each opioid. Different opioids were not randomized between the groups because of the differing time courses of the experiments.

Respiratory depression was measured in terms of ventilatory frequency by recording respiratory pressure waveforms for each ventilatory cycle on a Grass 79C polygraph recorder. This was done by gently hand-holding the mouse and placing its snout in the barrel of a 2-ml syringe, connected to a pressure transducer and recorder. Recordings were taken for not more than 10 s, to reduce the possibility of rebreathing carbon dioxide. The volumes of gas involved precluded the measure-

ment of carbon dioxide, but if rebreathing had occurred it would have been seen as an increase in ventilatory frequency and effort.

Analgesia was measured after ventilatory frequency by placing the mouse on a hot plate maintained at 55 °C and recording the time interval until the mouse showed a response—either jumping or lifting a hind leg off the plate. This was taken as an indication of analgesia. In order to prevent any tissue damage, mice were removed from the hot plate after 45 s without response. Readings for analgesia and respiratory depression were taken at suitable intervals, which varied according to the time course of action of the drugs, which had been determined by prior experimentation. With the exception of control mice, readings were continued until the hot plate reaction times had returned to pre-drug values. In time-effect relationships, the results from all drug treated mice were compared with concurrently tested vehicle control mice.

Significance ($P < 0.05$) was assessed using the Mann-Whitney *U* test although, for clarity, mean values (SE) are shown in the figures. Correlations were sought only on paired values of hot plate reaction times and ventilatory frequency changes that demonstrated significant increases in reaction time over concurrently tested saline control mice. In addition, all pairs of values containing hot plate reaction times which were greater than 45 s were excluded from calculations of the correlation coefficients.

Fentanyl, sufentanil and alfentanil were diluted in saline from prepared ampoules (donated by Janssen Pharmaceuticals Ltd). Morphine hydrochloride (Macfarlane Smith Ltd) and etorphine hydrochloride (a gift from Reckitt and Colman Ltd) were prepared by dissolving the dry powder in saline.

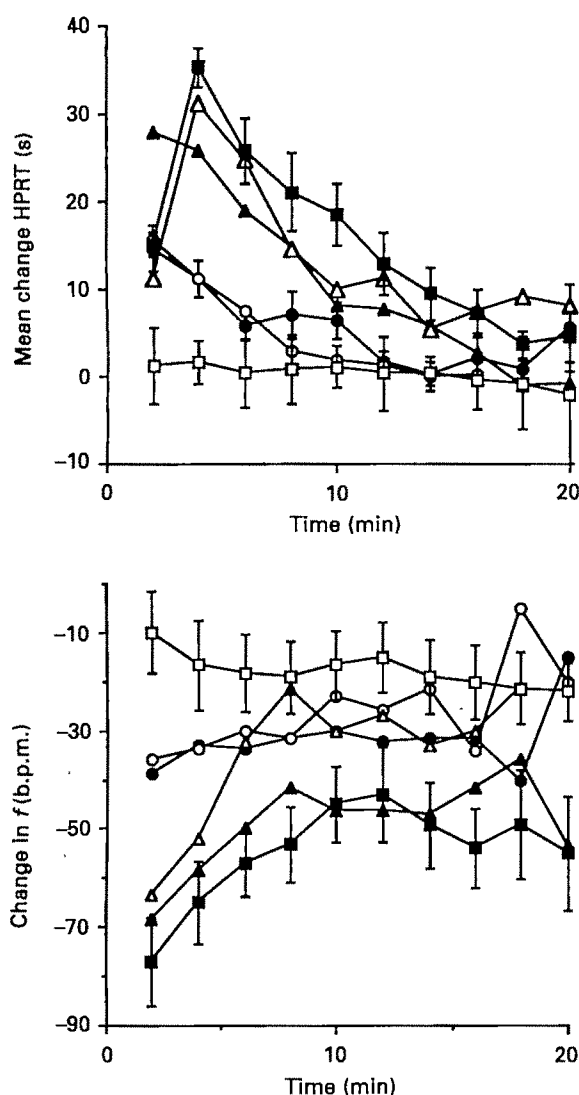


FIG. 1. Time course of the effects of alfentanil on hot plate reaction time (HPRT) and ventilatory frequency (f) in mice measured as change from pre-drug control values. Mean values ($n = 12$) of mice given saline ($\square$) or alfentanil 0.125 mg kg^{-1} ($\bullet$), 0.25 mg kg^{-1} ($\circ$), 0.5 mg kg^{-1} ($\blacktriangle$), 0.6 mg kg^{-1} ($\triangle$) and 0.8 mg kg^{-1} ($\blacksquare$). A few representative SE are shown.

RESULTS

In the fentanyl and alfentanil groups, there was rapid onset of profound analgesia and respiratory depression which was relatively short lived and dose dependent. The time-response relationships for alfentanil are shown in figure 1. Although alfentanil produced significant analgesia and respiratory depression, there was no correlation

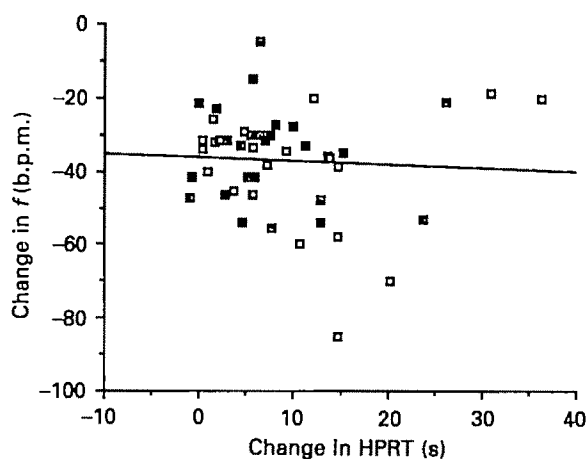


FIG. 2. Alfentanil treated mice. Relationship between change in hot plate reaction time (HPRT) and ventilatory frequency (f) depression showing no simple linear correlation ($y = -36.240 - 9.6699e-2x$; $r^2 = 0.003$).

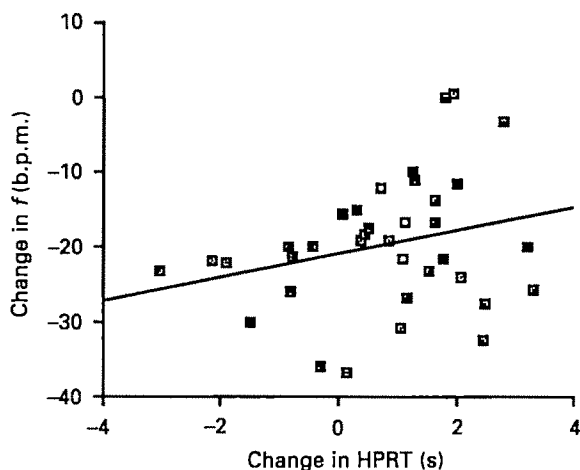


FIG. 3. Saline treated control mice. Relationship between change in hot plate reaction time (HPRT) and ventilatory frequency (f) depression, showing no simple linear correlation ($y = -20.933 + 1.5577x$; $r^2 = 0.073$).

between these two variables (fig. 2). A similar correlation was obtained in saline control animals, which showed no significant changes from pre-drug hot plate reaction times and ventilatory frequencies (fig. 3). At the other extreme were the results for etorphine, for which there was a strong correlation between analgesia and respiratory depression (fig. 4), although the shapes of the time-effect relationships and the maximum responses obtained (fig. 5) were similar for those recorded for alfentanil (fig. 1). Intermediate

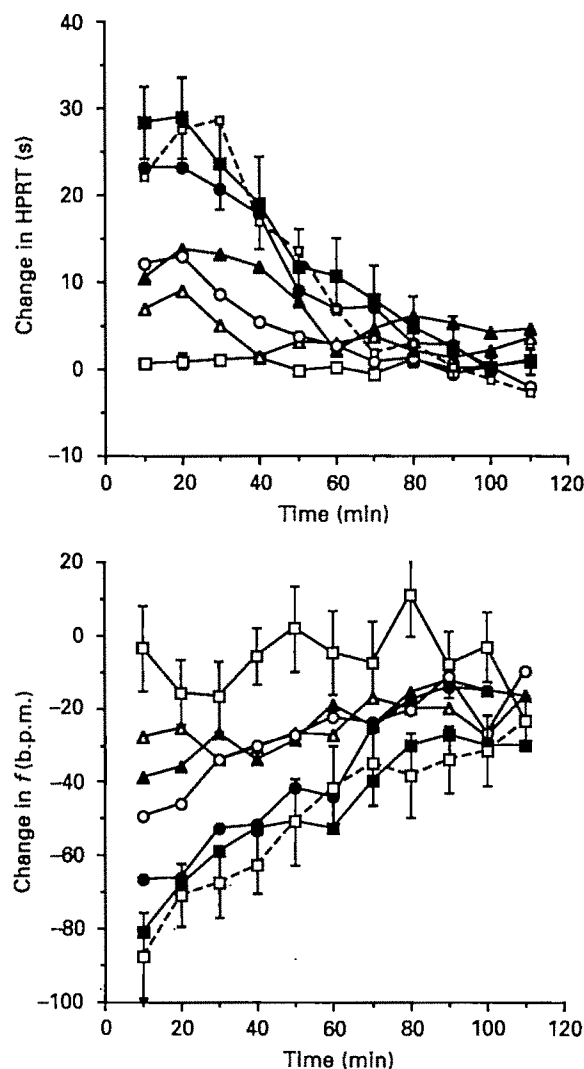


FIG. 4. Time course of the effects of etorphine on hot plate reaction time (HPRT) and ventilatory frequency (f) in mice measured as change from pre-drug control values. Mean values ($n = 12$) of mice given saline ($\square$) or etorphine $2 \mu\text{g kg}^{-1}$ ($\triangle$), $4 \mu\text{g kg}^{-1}$ ($\blacktriangle$), $5 \mu\text{g kg}^{-1}$ ($\circ$), $8 \mu\text{g kg}^{-1}$ ($\bullet$), $10 \mu\text{g kg}^{-1}$ ($\blacksquare$) and $15 \mu\text{g kg}^{-1}$ ($\square$). A few representative SE are shown.

TABLE II. Correlation coefficients between ventilatory frequency and hot plate reaction time, and mu over delta selectivity for some opioid drugs

Drug	Correlation coefficient (%)	Mu selectivity
Etorphine	76.9	0.5 [9]
Sufentanil	54.2	24.9 [7]
Fentanyl	52.4	82.5 [7]
Morphine	38.9	122.0 [7]
Alfentanil	0.3	602.0 [7]

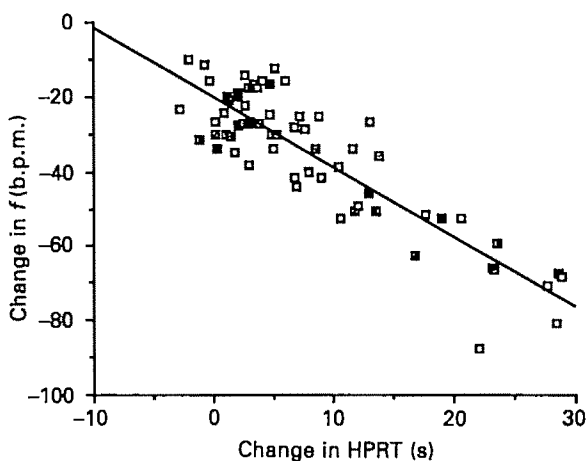


FIG. 5. Etorphine treated mice. Relationship between change in hot plate reaction time (HPRT) and ventilatory frequency (f) depression, showing a strong simple linear correlation ($y = -20.018 - 1.8735x$; $r^2 = 0.769$).

correlations were obtained for sufentanil, fentanyl and morphine. The correlation coefficients for these and other opioids, together with their mu-delta selectivity are shown in table II.

DISCUSSION

Etorphine, which showed the strongest correlation between analgesia and respiratory depression, demonstrates a relative affinity for mu, delta and kappa receptors of 0.2, 0.4 and 1.0, respectively [9]. This implies that etorphine has little selectivity for any one of the opioid receptors; indeed, it has been termed the universal ligand for opioid receptors [8].

Alfentanil, however, which is highly selective for the mu receptor, showed a weak correlation between analgesia and respiratory depression (0.3%). In the opioids tested in this study, weaker correlations appeared to be associated with higher mu receptor selectivity.

Most of the values for selectivity for the mu site (table II) came from a study in which only mu and delta receptor binding were considered. Thus it may be that kappa binding could influence the results. However, kappa receptor agonists are usually considered to be inactive when radiant heat, such as the hot plate, is used as the noxious stimulus [10]. Although Shaw, Rourke and Burns [11] have disputed the suggestion that various receptor-selective agonists have specificity for a particular modality of pain, they agree that kappa

agonists show little activity when the hot plate temperature is as great as 55 °C. In addition, of the three main opioid receptor types, there is least evidence that kappa receptors are involved in respiratory depression, although a modulatory role can not be excluded [12]. This evidence gives some support for concentrating on mu and delta receptor activity to explain the results obtained in the present study.

It has been suggested that mu and delta receptors may exist in two forms, either complexed together or separate [13, 14]. Both mu and delta receptor activation appear to produce analgesia at the supraspinal [15] and spinal levels [16] and activation of delta receptors enhances the response of activation of mu receptors in the complexed receptor [17]. Involvement of the mu-delta receptor complex may be important also in the control of ventilation, as there is evidence that mu receptor activation is necessary before delta receptor activation leads to respiratory depression [6]. Thus it may be that drugs with significant mu and delta activity act preferentially at the mu-delta receptor complex where the two activities cause enhanced analgesia and respiratory depression. More selective mu agonists may act either at the complexed or non-complexed mu receptor. The latter may be identical to the mu 1 receptor [13] which has been associated by some with analgesia, but not respiratory depression [3]. If this is the case, the relationship between analgesia and respiratory depression for these agents may be less predictable.

It is possible, however, that other factors contribute to the correlations obtained. Opioid drugs differ in their lipid solubility, degree of ionization at physiological pH and protein binding, all of which contribute to pharmacokinetic differences which influence their potency and duration of action [18]. Morphine, alfentanil and fentanyl have been compared with respect to these characteristics [18] and, although the rank order of individual measures differs from those of the correlation coefficients described in the present study, combinations of these properties could influence the results obtained.

REFERENCES

1. Eckenhoff JE, Oech SR. The effects of narcotics and antagonists upon respiration and circulation in man. *Clinical Pharmacology and Therapeutics* 1960; 1: 483-524.
2. McGilliard KL, Takemori AE. Antagonism by naloxone of narcotic induced respiratory depression and analgesia. *Journal of Pharmacology and Experimental Therapeutics* 1978; 207: 494-503.
3. Ling GSF, Spiegel K, Nishimura SL, Pasternak GW. Dissociation of morphine's analgesic and respiratory depressant actions. *European Journal of Pharmacology* 1983; 86: 487-488.
4. Ward SJ, Takemori AE. Determination of the relative involvement of mu opioid receptors in opioid-induced depression of respiratory rate by use of β -funaltrexamine. *European Journal of Pharmacology* 1983; 87: 1-6.
5. Rourke JD, Shaw JS. Failure to demonstrate mu-isoreceptors. *Neuropeptides* 1984; 5: 85-88.
6. Freye E, Schnitzler M, Traub M. Opioid induced respiratory depression and antinociception are mediated by different subreceptors. In: Cros J, Meunier J-C, Hamon M, eds. *Progress in Opioid Research. Advances in the Biosciences* 1989; 75: 463-466.
7. Yeadon M, Kitchen I. Comparative binding of mu and delta selective ligands in whole brain and pons/medulla homogenates from rat: affinity profiles of fentanyl derivatives. *Neuropharmacology* 1988; 27: 345-348.
8. Casey FC, Parfitt RT. *Opioid Analgesics—Chemistry and Receptors*. London: Plenum Press, 1986; 356.
9. Paterson SJ, Robson LE, Kosterlitz HW. Classification of opioid receptors. *British Medical Bulletin* 1983; 39: 31-36.
10. Tyers MB. Studies on the antinociceptive activities of mixtures of μ - and κ -opiate receptor agonists and antagonists. *Life Sciences* 1982; 31: 1233-1236.
11. Shaw JS, Rourke JD, Burns KM. Differential sensitivity of antinociceptive tests to opioid agonists and partial agonists. *British Journal of Pharmacology* 1988; 95: 578-584.
12. Yeadon M, Kitchen I. Opioids and respiration. *Progress in Neurobiology* 1989; 33: 1-16.
13. Heyman JS, Jiang Q, Rothman RB, Mosberg HI, Porreca F. Modulation of μ mediated antinociception by δ agonists: characterization with antagonists. *European Journal of Pharmacology* 1989; 169: 43-52.
14. Rothman RB, Lon JB, Bykov V, Jacobson AC, Rice KC, Holaday JW. Pretreatment of rats with the irreversible μ receptor antagonist β -FNA, fails to prevent naltrexone-induced up regulation of μ opioid receptors. *Neuropharmacology* 1990; 29: 805-810.
15. Heyman JS, Vaught JL, Raffa RB, Porreca F. Can supraspinal δ -opioid receptors mediate antinociception? *Trends in Pharmacological Sciences* 1988; 9: 134-138.
16. Dickenson AH, Sullivan AF, Knox R, Zajac JM, Roques BP. Opioid receptor subtypes in the rat spinal cord: electrophysiological studies with μ and δ receptor agonists in the control of nociception. *Brain Research* 1987; 413: 36-44.
17. Vaught JL, Rothman RB, Westfall TC. Mu and delta receptors: their role in analgesia and in the differential effects of opioid peptides on analgesia. *Life Sciences* 1982; 30: 1443-1455.
18. Hull CJ. The pharmacokinetics of alfentanil in man. *British Journal of Anaesthesia* 1983; 55: 157S-164S.

MODIFICATION BY DRUGS USED IN ANAESTHESIA OF CNS STIMULATION INDUCED IN MICE BY LAUDANOSINE AND STRYCHNINE†

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SUMMARY

We have investigated in mice the effects of several drugs which may be administered as part of an anaesthetic technique on the convulsive threshold to laudanosine and to strychnine, which is reported to have a similar mechanism of action. I.v. administered propofol, thiopentone and midazolam increased the dose of convulsant necessary to produce seizure when administered 2 min before the convulsive stimulus. In contrast, methohexitone and etomidate exhibited a pro-convulsant effect, although with the latter this was significant only in laudanosine-treated mice. Pethidine was proconvulsant in both laudanosine- and strychnine-treated mice, but morphine was proconvulsant only in strychnine-treated mice. The effects of morphine, but not pethidine, were antagonized by naloxone 1 mg kg⁻¹. Laudanosine, but not strychnine caused arousal from anaesthesia in subconvulsive doses. This and other evidence suggests that the mechanism of the CNS excitation produced by strychnine and laudanosine are not the same.

KEY WORDS

Anaesthetics, Intravenous: methohexitone, etomidate, propofol, thiopentone. Analgesics: morphine, pethidine. Complications: convulsions, laudanosine, strychnine.

Laudanosine is one of the major breakdown products of the neuromuscular blocking agent atracurium [1] and has been shown to have potent convulsive action in dogs [2] and rats [3]. Many agents used during anaesthesia have both pro- and anticonvulsant activity. For example, barbiturates such as phenobarbitone may be anticonvulsant at doses causing little sedation, and others such as methyl-thiobutobarbitone have so many excit-

atory effects such as gross limb movement that their use as anaesthetic agents is not feasible [4]. The clinically useful i.v. anaesthetics have activity profiles between these two extremes. The isomer of methohexitone marketed as an i.v. anaesthetic is the alpha-DL isomer, as the beta isomer had too much intrinsic excitatory activity to be clinically useful. Even so, methohexitone as marketed has been reported to have more proconvulsant activity than thiopentone. Indeed, methohexitone has been used to provoke epileptiform activity in patients with seizure patterns that were not revealed by awake records [5]. In contrast, thiopentone is reported not to provoke an epileptic response in such patients [6]. Nevertheless, many authors do not feel that methohexitone is contraindicated in patients with epilepsy [7-9] and its use to control seizures has been advocated by some [4]. Similar controversy exists concerning the pro- and anticonvulsant profile of other drugs used in anaesthesia. Midazolam, with pronounced anticonvulsant properties [10], has been reported to produce seizures in several instances [11]. Propofol has been reported to reduce the duration of ECT-induced seizures [12-14] and to be a useful agent in status epilepticus [15]. Despite these reports, several case reports have appeared in the literature reporting convulsions, opisthotonus or epileptiform EEG activity in patients given

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propofol [16, 17]. In addition, opioid drugs and endogenous peptides have been implicated in pro- and anticonvulsant activity [18].

Avramov and Mori [19] have demonstrated that nitrous oxide antagonizes the CNS stimulating action of laudanosine and this raises the question as to how other drugs used in anaesthesia might modify the excitatory action of laudanosine. The present study was designed to investigate this question in the experimental animal. A range of i.v. induction agents have been used, together with midazolam and the opioid drugs morphine and pethidine. Morphine was selected as the standard opioid drug with which others are compared and pethidine was chosen as it is particularly prone to excitatory side effects [20].

The mechanism of the excitatory action of laudanosine is uncertain, but is thought to be related to antagonism of glycine receptors in a manner similar to that for strychnine [21]. This was supported by the later work of Pong and Graham [22] using rat electroretinography as a screen for glycine antagonists. Since Soar and colleagues [23] have implicated glycine antagonism in the excitatory actions of some i.v. anaesthetic agents, it was decided to compare the interactions of laudanosine and drugs used in anaesthesia with those of the standard glycine antagonist, strychnine.

MATERIALS AND METHODS

Female MF1 mice weighing 25–35 g were used in the study, which was approved by the Home Office under the Animals (Scientific Procedures) Act 1986 (licence number 50/00609). All experiments were carried out between 10:00 and 14:00. Each mouse was weighed and injected with opioid drug, i.v. anaesthetic agent or vehicle. The opioids were injected i.p. (0.1 ml per 10 g body weight) 15 min before testing and the i.v. drugs were injected (0.1 ml per 10 g body weight) into the lateral tail vein over a 10-s period 2 min before testing. I.v. injections were carried out using a winged-needle infusion set (Butterfly-27, Abbott Laboratories Ltd) with an outside diameter of 0.4 mm and length of 9.5 mm attached to a 1-ml syringe. All i.v. injections took place in a specially designed box which allowed movement of the mouse with the exception of the tail, which was gently held. The minimum convulsant dose for laudanosine and strychnine was obtained by infusing the convulsant agent at a rate of

0.12 ml min⁻¹ into a second tail vein until a full seizure occurred, at which point the animal was killed immediately by an overdose of anaesthetic before consciousness returned. The dose was calculated as the total dose of convulsant infused divided by body weight. The dose that induced arousal from anaesthesia was noted also in the relevant experiments. In all experiments, the results from drug-treated mice were compared with those for vehicle-treated mice which were tested concurrently using randomly selected cage mates. A single observer was responsible for all animals tested in a given drug group—for example all morphine experiments or all thiopentone experiments. Doses of drugs were selected which had significant pharmacological activity in the mouse. Usually, these data were obtained from previous studies by this anaesthetic research group and are compatible with the literature. In preliminary experiments at least two doses of each i.v. anaesthetic were selected: a small dose which anaesthetized all mice within 10 s and induced sleeping times of 3–5 min, and a larger dose which induced 7–10 min sleep with no fatalities. Insufficient data were produced in these dose finding studies to analyse statistically the sleeping time results.

Laudanosine (Sigma Chemical Co.) and strychnine (BDH) were dissolved in 0.9% saline using an ultrasonic shaker and a few drops of hydrochloric acid 1 mol litre⁻¹ and adjusted to pH 6.8 with sodium bicarbonate. The final concentrations for infusion were 2 mg ml⁻¹ for laudanosine and 100 µg ml⁻¹ for strychnine.

Thiopentone (Intraval Sodium, May & Baker Pharmaceuticals) and methohexitone (Brietal, Eli Lilly & Co., Ltd) were prepared freshly every day from the commercially available ampoules by dissolving the dry powder in saline. Propofol (Diprivan, ICI Pharmaceuticals) and etomidate (Hypnomidate, Janssen Pharmaceuticals Ltd) were diluted with normal saline immediately before injection, dilutions of Intralipid (Kabi Vitrum) or propylene glycol (BDH) being used as the vehicle control. Morphine hydrochloride (Macfarlane Smith Ltd) and midazolam (Roche Products Ltd) were prepared by dissolving the dry powder in saline, whilst pethidine was diluted with normal saline from pethidine injection 50 mg ml⁻¹ (MacCarthys Ltd). Although results are described as mean values (SEM) (unless otherwise stated, $n = 10$) for ease of presentation, statistical comparisons were performed using the

Mann-Whitney *U* test to avoid assumptions on the distribution of data.

RESULTS

In saline-treated control animals, laudanosine i.v. caused no visible behavioural changes until seizures occurred with a dose of 16.1 (0.5) mg kg⁻¹. The seizure consisted of an asymmetrical clonic convulsion which proceeded into a tonic phase if the animal was not killed immediately after the appearance of the convulsion. In contrast, strychnine induced a seizure characterized by symmetrical tonic extension of the body and limbs with no evidence of a clonic phase; the dose necessary was 0.61 (0.02) mg kg⁻¹. In the presence of the anaesthetic agents, laudanosine, but not strychnine, caused arousal before the onset of the convulsion. Arousal in the mice given the larger doses of anaesthetic agent occurred when about 50% of the convulsant dose had been injected (table I). (In the lower dose experiments arousal and natural waking could be confused.)

Thiopentone induced anaesthesia in mice with no abnormal movements of the limbs. Two minutes after the administration of thiopentone, the dose of laudanosine necessary to induce

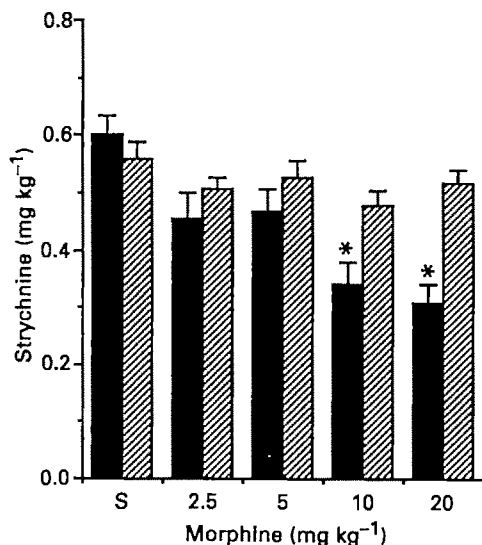


FIG. 1. Effect of i.p. morphine on the convulsant dose of strychnine alone (■) and in the presence of naloxone 1 mg kg⁻¹ (▨) in mice. Mean (SE) of groups of 10 mice. The saline control (S) corresponding to the largest dose of morphine is shown. *Significantly different from concurrently tested control group ($P < 0.05$).

TABLE I. Dose of i.v. laudanosine necessary to produce arousal in mice anaesthetized with thiopentone, methohexitone, propofol or etomidate. Mean values (SE) of groups of 10 mice

Drug	Dose (mg kg ⁻¹)	Arousal dose of laudanosine (mg kg ⁻¹)
Thiopentone	40	7.8 (0.7)
Methohexitone	20	8.7 (0.8)
Propofol	30	8.0 (0.7)
Etomidate	6.7	8.1 (0.9)

TABLE II. Effect of i.v. thiopentone, methohexitone, propofol, etomidate and midazolam on the convulsant dose of laudanosine and strychnine in mice. Mean values (SE) of groups of 10 mice. The saline or vehicle control corresponding only to the largest dose of anaesthetic or midazolam is shown for clarity. *Significantly different from concurrently tested control group ($P < 0.05$)

Drug	Laudanosine (mg kg ⁻¹)	Strychnine (mg kg ⁻¹)
Thiopentone		
0 (Saline)	15.5 (0.9)	0.724 (0.029)
30 mg kg ⁻¹	17.9 (0.9)	0.751 (0.028)
40 mg kg ⁻¹	19.2 (1.0)*	0.783 (0.032)
Methohexitone		
0 (Saline)	17.4 (0.5)	0.707 (0.021)
10 mg kg ⁻¹	22.7 (0.5)	0.699 (0.020)
20 mg kg ⁻¹	13.7 (0.3)*	0.447 (0.028)*
Propofol		
0 (Vehicle)	18.5 (0.6)	0.630 (0.022)
10 mg kg ⁻¹	23.4 (1.1)*	0.800 (0.018)*
20 mg kg ⁻¹	26.9 (1.5)*	0.900 (0.019)*
30 mg kg ⁻¹	28.7 (0.6)*	1.080 (0.061)*
Etomidate		
0 (Vehicle)	17.5 (0.6)	0.725 (0.039)
2.5 mg kg ⁻¹	21.8 (0.5)*	0.732 (0.042)
5 mg kg ⁻¹	18.7 (1.0)	0.719 (0.054)
6.7 mg kg ⁻¹	14.2 (0.9)*	0.745 (0.062)
Midazolam		
0 (Saline)	15.5 (0.9)	0.920 (0.033)
20 mg kg ⁻¹	29.3 (1.2)*	1.160 (0.026)*
30 mg kg ⁻¹	32.0 (1.0)*	1.160 (0.039)*

convulsions was significantly increased (table II). Additional experiments showed that this protective effect outlasted the anaesthetic action of the drug as, 15 min after injection of thiopentone 40 mg kg⁻¹, the convulsive dose of laudanosine had increased further to 25.1 (1.3) mg kg⁻¹. Thiopentone in doses up to 40 mg kg⁻¹ had no protective effect against strychnine-induced seizures.

In contrast, methohexitone reduced the doses of both strychnine and laudanosine necessary to

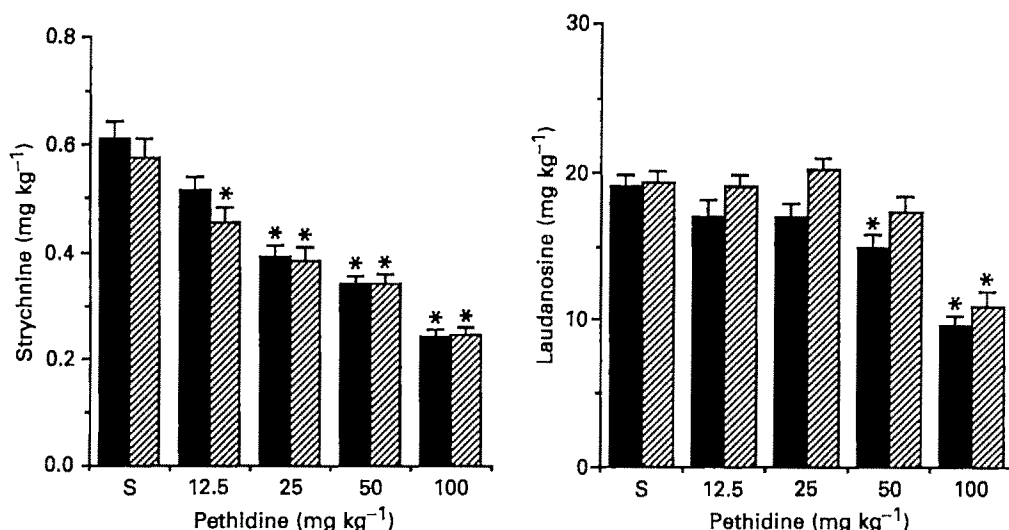


FIG. 2. Effect of i.p. pethidine on the convulsant dose of laudanose and strychnine alone (■) and in the presence of naloxone 1 mg kg⁻¹ (▨) in mice. Mean values (SE) of groups of 10 mice. The saline control (S) corresponding to the largest dose of pethidine is shown. *Significantly different from concurrently tested control group ($P < 0.05$).

induce convulsions, this being significant with the 20 mg kg⁻¹ dose (table II). However, this dose of methohexitone produced anaesthesia with visible cyanosis. Smaller doses were not proconvulsant and, indeed, the 10-mg kg⁻¹ dose significantly protected mice against laudanose-induced seizures, even though the mice exhibited myoclonic jerks and opisthotonus in response to the anaesthetic agent alone. A similar pattern of responses was seen with etomidate and laudanose (table II), in that 6.7 mg kg⁻¹ had a proconvulsant effect, whilst the smaller dose was protective against laudanose-induced convulsions but caused twitching and myoclonic jerks when administered alone. An intermediate dose of etomidate (5 mg kg⁻¹) was tested to determine the dose at which the changeover from anticonvulsant to proconvulsant effects occurred. No opisthotonus occurred with etomidate. In contrast with methohexitone, the proconvulsant dose of etomidate in laudanose-infused mice had no significant effects in strychnine-infused mice.

Propofol produced a dose-dependent anticonvulsant effect against both compounds (table II). An additional dose of propofol, which induced an unsteady gait but no loss of righting reflex, still produced an anticonvulsant effect. The largest dose caused anaesthesia with visible cyanosis. No abnormal limb movements were seen when propofol was administered i.v.

Midazolam also was anticonvulsant in both seizure models (table II), although it clearly provided greater protection against laudanose than strychnine.

Morphine 2.5–20 mg kg⁻¹ had no effect on laudanose-induced convulsions, but produced a dose-dependent proconvulsant effect in mice infused with strychnine. This effect was abolished by the administration of naloxone 1 mg kg⁻¹ (fig. 1). Pethidine was proconvulsant in both seizure models—an action which was unaffected by administration of naloxone (fig. 2).

DISCUSSION

Many anticonvulsant drugs increase gamma amino-butyric acid (GABA) concentrations or enhance inhibitory transmission through GABA_A receptors [24] and this may explain the anticonvulsant actions demonstrated for many agents in this study. Propofol at anaesthetically relevant concentrations enhances GABA-mediated transmission [25], as do other anaesthetic agents including the barbiturates, etomidate and the benzodiazepines [26].

The two i.v. anaesthetic agents associated most often with excitatory phenomena, etomidate and methohexitone, have been shown to possess significant proconvulsant activity. However, this proconvulsant activity was not seen with small

doses of these agents which produce the most obvious excitatory effects.

Soar and colleagues [23] proposed that methohexitone and propofol might exert excitatory effects by virtue of glycine antagonism, as their excitatory effects were potentiated by low doses of the glycine antagonist, strychnine, but not by low doses of bicuculline, an antagonist at GABA_A receptors. Whilst the present work with methohexitone is compatible with this conclusion, no proconvulsant effects were detected for propofol, even when strychnine was the convulsive stimulus. Indeed, propofol was convincingly anticonvulsant in this seizure model. However, there are many methodological differences between the two series of experiments, the most important probably being the route of injection. The present study used exclusively the i.v. route, whilst Soar and colleagues' [23] experiments used the i.p. route. With the latter, much greater whole body doses are required to produce anaesthesia, the concentrations in the biophase remain increased for longer and a greater degree of metabolism will have occurred. In addition, when a drug is given i.p., the progression towards anaesthesia is slower and an excitatory action may be revealed which would have been swamped by an anticonvulsant action if the drug was given i.v. An anticonvulsant action of i.v. propofol against strychnine-induced convulsions has been demonstrated by Hogskilde [unpublished data on file, ICI Pharmaceuticals]. In patients with epilepsy, etomidate has been reported to have proconvulsive activity [27-29], whilst in other circumstances it is anticonvulsant [30]. In the present study, it was possible to demonstrate a proconvulsant action for etomidate only when laudanose was the convulsive stimulus; even then, the effect obtained was dependent upon the dose used. Etomidate had no effect on strychnine-induced seizures and was anticonvulsant in pentylenetetrazole-induced seizures [31].

It is clear that laudanose- and strychnine-induced convulsions differ both in their gross characteristics and in the way they are modified by drugs used in anaesthesia. This indicates that there is not a common mechanism for the seizures produced by the two convulsant agents. Neither opioid tested exhibited any anticonvulsant activity: pethidine was proconvulsant in both seizure models, whilst morphine was proconvulsant only in the strychnine model. The proconvulsant action of morphine in strychnine-treated animals

was naloxone sensitive and probably involves classical opioid receptors. A similar interaction between morphine and strychnine has been reported in other species [18].

Pethidine and morphine have a similar selectivity for the subtypes of opioid receptors [32]. However, pethidine or, more likely, its metabolite norpethidine has been shown to be a convulsant in man and animals and this effect is potentiated by naloxone [20]. Thus it is not surprising that the proconvulsant activity of pethidine described in the present work was not naloxone sensitive. It is probable also that pethidine is not exerting its effects through opioid receptors. Pethidine-induced hypothermia in the mouse is also insensitive to naloxone and an involvement of tryptaminergic mechanisms has been proposed [33]. The involvement of tryptaminergic mechanisms in the proconvulsant action of pethidine has yet to be investigated.

REFERENCES

1. Chapple DJ, Clarke JS. Pharmacological action of breakdown products of atracurium and related substances. *British Journal of Anaesthesia* 1983; 55 (Suppl. 1): 11S-15S.
2. Hennis PJ, Fahey MR, Canfell PC, Shi WZ, Miller RD. Pharmacology of laudanose in dogs. *Anesthesiology* 1986; 65: 56-60.
3. Scheepstra GL, Vree TB, Crui JF, Van de Pol F, Reekers Ketting J. Convulsive effects and pharmacokinetics of laudanose in the rat. *European Journal of Anaesthesiology* 1986; 3: 371-383.
4. Dundee JW, Wyant GM. *Intravenous Anaesthesia*, 2nd Edn. Edinburgh: Churchill Livingstone, 1988.
5. Pampiglione G. Very short acting barbiturate (methohexital) in the detection of cortical lesions. *Electroencephalography and Clinical Neurology* 1965; 19: 314.
6. Paul R, Harris R. A comparison of methohexitone and thiopentone in electrocortography. *Journal of Neurology, Neurosurgery and Psychiatry* 1970; 33: 100-104.
7. Whitwam JD. The pharmacology of brietal sodium (methohexital). *Das Ultrakurznnarkotikum Methohexital. Anaesthesia and Resuscitation* 1972; 57: 2-8.
8. Moreland F, Sture C, Wood R. Methohexitone and epilepsy. *British Dental Journal* 1969; 126: 297.
9. Allen EM, Male CG. Methohexital is not contraindicated in epileptics. *Anesthesiology* 1982; 56: 240-241.
10. Pieri L. Preclinical pharmacology of midazolam. *British Journal of Clinical Pharmacology* 1983; 16: 17S-27S.
11. Engstrom RH, Cohen SE. A complication associated with the use of midazolam. *Anesthesiology* 1989; 70: 719.
12. Simpson KH, Halsall PJ, Carr CME, Stewart KG. Propofol reduces seizure duration in patients having anaesthesia for electroconvulsive therapy. *British Journal of Anaesthesia* 1988; 61: 343-344.
13. Dwyer R, McCaughey W, Lavery J, McCarthy G, Dundee JW. Comparison of propofol and methohexitone

- as anaesthetic agents for electroconvulsive therapy. *Anaesthesia* 1988; 43: 459-462.
14. Rampton AJ, Griffin RM, Stuart CS, Durcan JJ, Huddy NC, Abbott MA. Comparison of methohexital and propofol for electroconvulsive therapy: Effects on hemodynamic response and seizure duration. *Anesthesiology* 1989; 70: 412-417.
 15. Wood PR, Browne GPR, Pugh S. Propofol infusion for the treatment of status epilepticus. *Lancet* 1988; 1: 480-481.
 16. Hodgkinson BP, Frith RW, Mee EW. Propofol and the electroencephalogram. *Lancet* 1987; 2: 1518.
 17. Hopkins CS. Recurrent opisthotonus associated with anaesthesia. *Anaesthesia* 1988; 43: 904.
 18. Frenk H. Pro- and anticonvulsant actions of morphine and endogenous opioids: involvement and interaction of multiple opiate and non-opiate systems. *Brain Research Reviews* 1983; 6: 197-210.
 19. Avramov MN, Mori K. Nitrous oxide antagonizes CNS stimulation by laudanoline in mice. *British Journal of Anaesthesia* 1990; 65: 704-707.
 20. Iturrisi CE, Umans JG. Pethidine and its active metabolite norpethidine. In: Bullingham RES, ed. *Clinics in Anaesthesiology (Opiate Analgesia)* 1983; 1: 123-138.
 21. Mercier F, Delphaut J. Sur les convulsions produites par la laudanoline. *Compte Rendus des Séances de la Société de Biologie et de ses Filiales (Paris)* 1935; 118: 168-170.
 22. Pong SF, Graham LT jr. A relatively simple differential screening test for GABA or glycine antagonists using rat electroretinography. *Archives Internationales de Pharmacodynamie et de Thérapie* 1976; 220: 275-286.
 23. Soar J, Smith MB, Morris PJ, Dolin SJ. Does glycine antagonism underlie the excitatory effects of propofol and methohexital? *British Journal of Anaesthesia* 1991; 66: 398P.
 24. Gale K. GABA in epilepsy: the pharmacologic basis. *Epilepsia* 1989; 30 (Suppl. 3): S1-S11.
 25. Collins GGS. Effects of the anaesthetic 2,6-diisopropylphenol on synaptic transmission in the rat olfactory cortex slice. *British Journal of Pharmacology* 1988; 95: 939-949.
 26. Keane PE, Biziere K. The effects of general anaesthetics on gabaergic synaptic transmission. *Life Sciences* 1987; 41: 1437-1448.
 27. Krieger W, Copperman J, Laxer KD. Seizures with etomidate anaesthesia. *Anesthesia and Analgesia* 1985; 64: 1226-1227.
 28. Ebrahim ZY, DeBoer GE, Luders H, Hahn JF, Lesser RP. Effect of etomidate on the electroencephalogram of patients with epilepsy. *Anesthesia and Analgesia* 1986; 65: 1004-1006.
 29. Ganchar S, Laxer KD, Krieger W. Activation of epileptogenic activity by etomidate. *Anesthesiology* 1984; 61: 616-618.
 30. Waquier A. Profile of etomidate: a hypnotic, anticonvulsant and brain protective compound. *Anaesthesia* 1983; 38 (Suppl.): 26-33.
 31. Al-Muhandis WM. The proconvulsant and anticonvulsant actions of drugs in anaesthesia (M.Sc. Thesis). Manchester: University of Manchester, 1990.
 32. Magnan J, Paterson SJ, Tavani A, Kosterlitz HW. The binding spectrum of narcotic analgesic drugs with differing agonist and antagonist properties. *Naunyn-Schmiedeberg's Archives of Pharmacology* 1982; 319: 197-205.
 33. Pleuvry BJ, Menon AM. A comparison of the effects of morphine and pethidine upon body temperature and the reversal of reserpine's effects upon body temperature in the mouse. *Journal of Pharmacy and Pharmacology* 1976; 28: 827-831.

DETERMINATION OF CONTAMINATION OF A CHEMICAL WARFARE-PROOF OPERATING THEATRE WITH VOLATILE ANAESTHETIC AGENTS AND ASSESSMENT OF ANAESTHETIC GAS SCAVENGING SYSTEMS

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SUMMARY

Three types of anaesthetic waste scavenging systems (active antipollution system, Papworth Block passive system and activated charcoal absorber system) were compared with a non-scavenging control to assess their effectiveness in reducing waste halothane concentrations in a chemical warfare-proof operating theatre. All three systems were found to reduce the level of pollution significantly.

KEY WORDS

Anaesthetics, volatile: trace concentrations. Equipment: exhaust systems.

The Association of Anaesthetists of Great Britain and Ireland has recommended [1] that scavenging systems should be installed in order to decrease the concentration of anaesthetic gases in the operating department environment and this recommendation has been endorsed by the Department of Health and Social Security [2]. A survey carried out by the Royal Air Force Institute of Community Medicine [3] revealed high concentrations of volatile agents (halothane and trichloroethylene) contaminating the atmosphere inside a chemical warfare-proof theatre and the adjoining collective protection area. The aim of our study was first to determine the contamination of the chemical warfare-proof operating theatre under simulated conditions and second to assess the efficiency of a variety of available anaesthetic gas scavenging systems.

METHODS

The tented operating theatre (closed down for protection against chemical agents) was used for the study during a field exercise. The approximate volume of the operating theatre was 98 m³. The floor plan of the theatre with operating tables is shown in figure 1. The air filtration units at the corner of the operating room provided a ventilation of 3.5 air changes per hour. Measurement of volatile agent pollution and evaluation of the scavenging devices were carried out under simulated anaesthetic conditions using mechanical ventilation. The Triservice Anaesthetic Apparatus [4] was used with a ventilator (Cape TC 50, Penlon) set at a tidal volume of 800 ml and a frequency of 12 b.p.m. On three occasions we studied 3-h sessions consisting of four simulated general anaesthetics of 45 min each. The halothane concentration was set at 1% for the first 30 min then 0.5% for the next 10 min, with halothane discontinued for the last 5 min of each anaesthetic. At the beginning of each anaesthetic, induction of anaesthesia and tracheal intubation were simulated by manually ventilating a "Resusci Ann" (Laerdal) with a face mask for 2 min. The Triservice anaesthetic apparatus was then connected to a lung simulator (BOC 314012).

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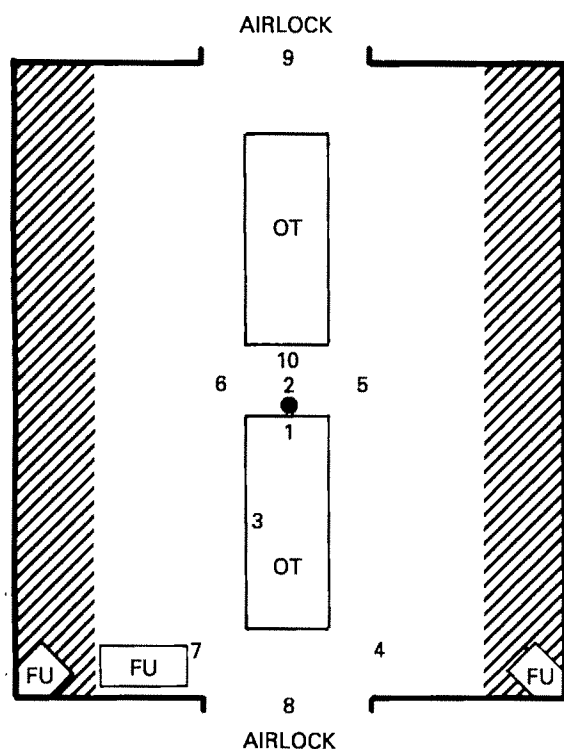


FIG. 1. Floor plan of operating theatre and sampling sites (not to scale). 1 = Patients's head; 2 = anaesthetist's nose level—standing; 3 = surgeon's nose level—standing; 4–7 = (nose levels standing) 91.5 cm diagonally from each corner of operating table; 8, 9 = doors; 10 = floor level—15 cm from ground; OT = operating tables; FU = air filtration unit; ▨ = tables with drugs and equipment; ● = simulated anaesthetic site.

The active antipollution system (Medishield No. 1355581), the Papworth Block passive system (Penlon Mk 2) and an activated charcoal absorber (Cardiff Aldasorber, Shirley Aldred) were tested for their efficiency in decreasing the trace concentration of anaesthetic vapour in the operating theatre. Only one operating table was used for the purpose of this study.

An infra-red analyser (Miran 1B) was calibrated using a closed loop system and with known volumes of halothane. The absorbance over a range of concentrations was used [5]. Measurements were taken at 10 predetermined sites (fig. 1) every 5 min throughout each session. Three sessions, one with no scavenging, and the remaining two with the active and passive scavenging systems, were studied. Sampling at site 10 was commenced only with the second 3-h simulated anaesthetic session.

In a further set of experiments, we studied another five sessions of 30 min. These sessions consisted of the administration of 1% halothane without scavenging (this being a shortened repeat of the earlier test as the theatre airflow had, by then, been changed: the airflow now was directed from door 8 to door 9 with similar air changes per hour), 3% halothane without scavenging, activated charcoal adsorption (Aldasorber) and passive and active scavenging systems. The sessions with the larger concentration of halothane were performed to simulate the volatile agent contamination that may occur with patients breathing spontaneously. In British military anaesthetic practice, nitrous oxide is not used in the field.

Ambient temperature, wind velocity and humidity remained similar on all three days of the study. Smoke studies did not show any pockets of pooling inside the theatre environment. The existing system of directional control of anaesthetic vapours via plastic drainage pipework fitted in the roof of the operating theatre was in operation during the entire study period. The vapours are flushed to ground level by air directed down from the fenestrated pipes, connected to the air filtration unit, that lie inside the tent.

Statistical methods

Normality of the raw data was assessed using standardized coefficients of skewness and kurtosis [6] and multiple box and whisker plots [7] (which also identified extreme outlying observations). Homogeneity of variance between compared groups was examined using the Bartlett's and Cochran's *C* tests (or the *F* test where only two groups were concerned) [6]. Transformations of the data were selected to normalize the data and stabilize group variances for use with parametric tests.

Both parametric and distribution-free summary statistics are reported.

The principal analysis was by multifactor analysis of covariance (ANACOVA), taking the treatment groups and sampling sites (in the operating theatre) as factors and time since the beginning of the operating session and the number of people in the operating theatre as covariates. Multiple range analysis was performed using 95% confidence intervals [8]. Available data concerning door opening and closing, times of vaporizer recharging, and starting and finishing times of consecutive operations were too limited to incorporate formally in the analysis. It is

anticipated that the results of the covariance analysis reflect these factors to some extent.

$P < 0.05$ was considered statistically significant.

Data analysis was performed using the Statgraphics computer software package [9].

RESULTS

In the first session of 3 h, a total of 279 samples were collected at the nine sites without scavenging. (An additional sampling site was included for the rest of the study.) In a similar manner, 360 and 330 samples were collected at 10 sites with passive and active scavenging systems in operation (table I). The initial outlying observation of 118 p.p.m. at site 1 in the non-scavenging group resulted from accidental spillage of halothane and has been omitted from analysis. The mean and

median concentrations of halothane in the operating theatre without scavenging were 7–10 times greater than those with active or passive scavenging systems. The percentages of observations above arbitrarily chosen concentrations of halothane are shown in table II, in which it may be seen that the halothane concentrations of all but two of the samples were greater than 5 p.p.m. and all were greater than 2 p.p.m. without scavenging. The percentages of samples less than or equal to the safety level recommended by the National Institute of Occupational Safety and Health [10] (2 p.p.m.) were 66.4% and 84.8% for passive and active scavenging systems, respectively. The corresponding figures for the Scandinavian statutory limit [11] of 5 p.p.m. were 95.3% and 97.6%.

Analysis was by multifactor ANACOVA of the reciprocal of the halothane concentrations (this transformation was selected as it improved the normality and stability of variance of the significantly non-normal raw data). Comparing the three individual groups (and omitting the site 10 readings), the time from start of each study session and the number of people in theatre, are significant covariates ($P < 0.001$). Taking these into account, the differences between the groups are significant ($P < 0.0001$). The halothane concentration in the non-scavenging group was significantly greater than in the passive and active scavenging groups ($P < 0.05$). The concentrations of halothane in the passive and active scavenging groups were not significantly different ($P > 0.05$). When only the passive and active groups were compared over all 10 sites (table I), concentrations were just significantly greater in the passive scavenging group ($0.01 < P < 0.05$).

For the 30-min study groups, both non-scavenging groups with 1% and 3% halothane showed a reduced mean concentration of halothane of 9.06 and 9.41 p.p.m., respectively and medians of 9.10 and 6.70 p.p.m. (compared with a mean of 14.94 p.p.m. and a median of 14.00 p.p.m. with the old air flow and nine sites) with the new air flow pattern (table III). The average concentrations of halothane with the passive and active systems with administration of 3% halothane did not seem to have increased from the values with 1% halothane. The paradoxical 26% decrease in the median concentration of halothane in the non-scavenging group which occurred when the administration of halothane was increased from 1 to 3%, could not be explained.

TABLE I. Halothane concentrations of pooled samples for the three sessions of 3 h duration each

Group	Sample size	Halothane concn (p.p.m.)	
		Mean (SD)	Median [range]
Non-scavenging	279	15.3 (8.1)	14.0 [4.9–118.0]
Non-scavenging (excluding one value 118 p.p.m.)	278	14.9 (5.2)	14.0 [4.9–34.0]
Passive			
Excluding site 10	324	2.2 (1.9)	1.7 [0.5–14.0]
10 sites	360	2.2 (1.8)	1.7 [0.5–14.0]
Active			
Excluding site 10	297	1.7 (1.1)	1.4 [0.8–9.7]
10 sites	330	1.7 (1.1)	1.4 [0.8–9.7]

TABLE II. Cumulative distribution of observations (obs.) in each of the three groups

Concentration (p.p.m.)	Percent of observations		
	Non-scavenging (278 obs.)	Passive scavenging (360 obs.)	Active scavenging (330 obs.)
> 0.5	100.0	99.4	100.0
> 1.5	100.0	54.4	32.1
> 2.0	100.0	33.6	15.2
> 5.0	99.3	4.7	2.4

TABLE III. Halothane concentrations of pooled data obtained from five sessions of 30 min duration

Group	Sample size	Halothane concn (p.p.m.)	
		Mean (SD)	Median [range]
Non-scavenging			
1% Halothane	60	9.1 (3.0)	9.1 [4.2-18.0]
3% Halothane	70	9.4 (8.0)	6.7 [0.7-43.0]
Passive scavenging	60	1.9 (1.1)	1.5 [0.6-4.2]
Active scavenging	60	1.6 (1.1)	1.3 [0.5-5.7]
Aldasorber	60	0.5 (0.4)	0.4 [0.0-1.3]

DISCUSSION

The determination of theatre pollution depends on the dispersal of anaesthetics, the sampling techniques and the method of analysis [12].

Although efforts were made to keep these conditions comparable in all sessions, some factors such as the opening of doors, the number of people in the operating theatre and the airflow pattern could not be kept constant.

Studies conducted within hospitals in the United Kingdom have found halothane concentrations ranging from 1.3 to 3.3 p.p.m. [13-15]. In our study the mean and median halothane concentrations were 15.3 and 14.0 p.p.m. for the 3-h period of study and 9.1 and 9.1 p.p.m. for the 30-min period of study, with no scavenging.

It may be argued that, in the event of a conflict requiring the mobilization of a field hospital, scavenging of waste anaesthetic gases would be lowest on the list of priorities. However, if a simple and effective system may be utilized without unduly affecting hospital personnel, it is beneficial to use it.

In our study, we found little difference in the performances of the active and passive scavenging systems in reducing environmental anaesthetic vapour pollution. Although we found the absorption system (Aldasorber) to be the most effective of the three in the short study period, the bulk of the system and the difficulty in resupply renders it unsuitable for field use. It is logical, therefore, to recommend the passive system of scavenging because of its simplicity, low weight, cost-effectiveness and satisfactory performance.

ACKNOWLEDGEMENTS

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REFERENCES

1. Association of Anaesthetists of Great Britain and Ireland. Advice to members from the council. Pollution of the atmosphere of operating theatres. *Anaesthesia* 1975; 30: 697.
2. Department of Health and Social Security. *Health Services Development. Pollution of Operating Department etc. by Anaesthetic Gases*. London: HMSO, 1976; Health Circular HC(76)38.
3. Royal Air Force Institute of Community Medicine. *A Report on an Anaesthetic Vapour Hazard in the Collective Chemical Protection Tentage No 2 Field Hospital*. 1984; Report ICM/91/84.
4. Houghton IT. The Triservice anaesthetic apparatus. *Anaesthesia* 1981; 36: 1094-1108.
5. Ilsley AH, Crea J, Cousins MJ. Evaluation of infrared analysers used for monitoring waste anaesthetic gas levels in operating theatres. *Anaesthesia and Intensive Care* 1980; 8: 436-440.
6. Snedecor GW, Cochran WG. *Statistical Methods*, 7th Edn. Ames, Iowa: Iowa State University Press, 1980.
7. Tukey JW. *Exploratory Data Analysis*. Reading, Massachusetts: Addison-Wesley, 1977.
8. Armitage P, Berry G. *Statistical Methods in Medical Research*, 2nd Edn. Oxford: Blackwell Scientific Publications, 1987.
9. Statistical Graphics Corporation. *Statgraphics Statistical Graphics System, Version 3.0*. USA: STSC Inc., 1988.
10. National Institute for Occupational Safety and Health. *Criteria for a Recommended Standard—Occupational Exposure to Waste Anaesthetic Gases and Vapours*. Cincinnati: U.S. Department of Health, Education and Welfare, 1977; DHEW publication No. (N105H)77-40.
11. *Arbejdstilsynets Liste over Hygiejniske Graensevaerdier* Copenhagen ø.: Arbejdstilsynet, 1981.
12. Smith WDA. Pollution and the anaesthetist. In: Langton Hewer C, Atkinson RS, eds. *Recent Advances in Anaesthesia and Analgesia*, Vol. 14. London: Churchill Livingstone, 1976; 131-173.
13. Thompson JM, Barratt RS, Hutton P, Robinson JS, Belcher R, Stephen WI. Ambient air contamination in a dental outpatient theatre. *British Journal of Anaesthesia* 1979; 51: 845-855.
14. Halliday MM, Carter KB, Davis PD, Macdonald D, Collins L, McCreddie G. Survey of operating room pollution within an NHS district. *Lancet* 1979; 1: 1230-1232.
15. Davenport HT, Halsey MJ, Wardley-Smith B, Bateman PE. Occupational exposure to anaesthetics in 20 hospitals. *Anaesthesia* 1980; 30: 354-359.

HAEMODYNAMIC EFFECTS OF PROPOFOL: INDUCTION WITH 2.5 MG KG⁻¹

J. E. FAIRFIELD, A. DRITSAS AND R. J. BEALE

SUMMARY

Serial measurements of haemodynamic variables were performed at 1-min intervals in nine ASA I, unpremedicated patients before and for 5 min after induction of anaesthesia with propofol 2.5 mg kg⁻¹. End-tidal carbon dioxide concentration was maintained within the normal range. Stroke volume and left ventricular function were measured by Doppler and cross-sectional echocardiography at the aortic valve. Systemic arterial pressure was measured by automated oscillometry and heart rate by electrocardiograph. Stroke volume, cardiac output, systemic vascular resistance, left ventricular stroke work and rate-pressure product were calculated. There was a decrease at all time points in systolic, mean and diastolic arterial pressure. There was an initial increase in heart rate and cardiac output, with a subsequent decrease to less than baseline. There was an initial decrease in systemic vascular resistance followed by partial recovery, and a delayed decrease in left ventricular function as measured by peak aortic blood flow velocity and acceleration.

KEY WORDS

Measurement techniques: Doppler ultrasound, echocardiography. Anaesthetics, intravenous: propofol.

Propofol has been shown consistently to cause a decrease in arterial pressure; decreases in both systemic vascular resistance and cardiac output have been reported. However, interpretation of some studies is complicated by the use of other drugs which affect the cardiovascular system, or the inclusion of patients with cardiovascular disease. We have used the technique of Doppler echocardiography, combined with automated non-invasive recording of arterial pressure to in-

vestigate the effects of an induction dose of propofol on the cardiovascular system of young, ASA I unpremedicated adults.

METHODS AND RESULTS

With Ethics Committee approval, we studied 15 unpremedicated ASA I patients undergoing extraction of wisdom teeth under general anaesthesia. Under local anaesthesia, a 16-gauge cannula was inserted into a large forearm vein. Baseline measurements of arterial pressure, heart rate and ascending aortic flow were made using a Datex Cardiocap non-invasive arterial pressure monitor, and a Vingmed Sonotron CFM 750 continuous wave Doppler echocardiograph. Ascending aortic blood flow was studied using a 1.9-MHz M-mode transducer positioned in the suprasternal notch.

Anaesthesia was induced with propofol 2.5 mg kg⁻¹ (mixed with lignocaine 0.125 mg kg⁻¹) given over 20 s. When consciousness was lost, 100% oxygen was administered via a Bain type coaxial breathing system. End-tidal carbon dioxide concentration was measured at the face mask using the Datex Cardiocap and ventilation was assisted to maintain the measured end-tidal carbon dioxide concentration constant. The electrocardiogram (with measured heart rate) was displayed continuously and arterial pressure was measured before induction and at 1-min intervals thereafter. The aortic blood velocity profile was recorded

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TABLE I. Mean values for all the measured and calculated haemodynamic variables (95% confidence intervals for the mean) before induction of anaesthesia with propofol 2.5 mg kg⁻¹ and at 1-min intervals for 5 min thereafter in nine patients, together with the probabilities, calculated by the paired *t* test, that the measured changes differ from baseline by chance alone

	Time after induction (min)					
	Baseline	1	2	3	4	5
Mean arterial pressure (mm Hg)	88 (83-92)	78 (68-88)	74 (68-79)	70 (62-78)	68 (62-74)	67 (63-71)
<i>P</i>		0.017	< 0.001	0.003	< 0.001	< 0.001
Heart rate (beat min ⁻¹)	71 (64-79)	81 (73-89)	72 (64-81)	71 (64-77)	65 (60-71)	65 (58-71)
<i>P</i>		0.037	0.70	0.83	0.053	0.012
Peak aortic blood velocity (m s ⁻¹)	1.18 (1.01-1.34)	1.26 (1.11-1.40)	1.13 (1.04-1.23)	1.10 (1.01-1.19)	1.05 (0.95-1.15)	1.10 (1.00-1.20)
<i>P</i>		0.13	0.48	0.14	0.031	0.14
Peak aortic blood acceleration (m s ⁻²)	19.5 (15.1-23.9)	20.4 (16.6-24.1)	19.3 (16.0-22.5)	18.9 (15.7-22.2)	18.4 (15.3-21.4)	18.5 (14.8-22.3)
<i>P</i>		0.11	0.70	0.37	0.18	0.14
Stroke volume (ml)	68.2 (59.9-76.5)	69.1 (61.4-76.8)	66.5 (59.8-73.2)	65.1 (58.4-71.9)	64.1 (57.5-70.8)	64.7 (56.4-73.0)
<i>P</i>		0.39	0.29	0.056	0.023	0.019
Cardiac output (litre min ⁻¹)	4.87 (4.15-5.59)	5.58 (5.00-6.16)	4.80 (4.30-5.31)	4.62 (4.02-5.21)	4.19 (3.78-4.59)	4.18 (3.74-4.62)
<i>P</i>		0.050	0.81	0.34	0.020	0.002
Systemic vascular resistance (dyn s cm ⁻⁵)	1505 (1224-1786)	1145 (947-1344)	1260 (1107-1413)	1261 (1043-1479)	1322 (1157-1486)	1323 (1128-1518)
<i>P</i>		0.005	0.029	0.042	0.079	0.023
Left ventricular stroke work (g m)	74.5 (67.9-81.2)	66.4 (57.3-75.4)	60.6 (55.4-65.7)	56.1 (50.1-62.1)	53.2 (47.5-58.8)	53.1 (46.9-59.3)
<i>P</i>		0.069	< 0.001	< 0.001	< 0.001	< 0.001
Rate-pressure product (beat min ⁻¹ mm Hg)	6324 (5466-7183)	6443 (5252-7633)	5474 (4492-6456)	5067 (4157-5977)	4524 (3757-5290)	4430 (3859-5001)
<i>P</i>		0.80	0.015	0.003	< 0.001	< 0.001

onto video tape for later analysis. After 5 min the study was concluded, an additional dose of propofol was administered and anaesthesia and surgery then proceeded as normal.

The video tape recordings of aortic blood flow made before induction and at 1, 2, 3, 4 and 5 min after induction were analysed. At each time point, mean values were derived for peak aortic blood velocity, peak aortic blood acceleration and aortic blood velocity integral. From the Doppler measured variables, measured aortic root diameter (which we assumed did not change during the course of the study), measured arterial pressure and measured heart rate, we were able to calculate stroke volume, left ventricular stroke work, cardiac output, systemic vascular resistance and rate-pressure product.

The data from four patients were not analysed: one because an additional dose of propofol was

required to induce anaesthesia, and three because the aortic flow measurements were technically unsatisfactory. Two other patients were very anxious, with pre-induction heart rates greater than 100 beat min⁻¹; data from these two patients are not included in the results.

The mean age of the nine patients (five male) for whom results are reported was 23 yr (95% confidence interval (CI) 20-26), mean weight 67 kg (95% CI 59-75).

Immediately after injection of propofol there was a marked reduction in systemic vascular resistance (32%), tachycardia (15%), and increased cardiac output (18%), but no significant change in stroke volume. The decrease in systemic vascular resistance predominated and the mean arterial pressure decreased (11%). There was a small increase in both peak aortic blood flow (8%) and acceleration (6%).

From about 2 min after injection of propofol and until the end of the study, systemic vascular resistance returned towards the resting value, but even after 5 min it was less than baseline (11%). The heart rate decreased to less than baseline (8%), despite the less than normal systemic vascular resistance. Stroke volume decreased slightly (5.5%) and there was a progressive reduction in cardiac output (15%). Mean arterial pressure decreased further (33%). Peak aortic blood acceleration and velocity decreased (3% and 9%, respectively). As would be expected from a simultaneous reduction in stroke volume, mean arterial pressure and heart rate, both the left ventricular stroke work and the rate-pressure product were reduced (28% and 29%, respectively).

Mean measured and derived haemodynamic variables for the group, 95% CI for the means and *P* values calculated for the difference from baseline using the paired *t* test (no allowance made for the effect of multiple tests) are presented in table I.

COMMENT

It is now well recognized that induction of anaesthesia with propofol causes a reduction in systemic arterial pressure, reportedly because of decrease in cardiac output [1], decrease in systemic vascular resistance [2], or both [3].

In this study we used the technique of Doppler aortic blood flow velocity measurement together with cross-sectional echocardiography to calculate stroke volume, peak aortic blood velocity and peak aortic blood acceleration. The principles and practice of the use of Doppler ultrasound for blood flow determination have been described previously [4].

Propofol appears to have a biphasic effect on the cardiovascular system. First, immediately after injection, the decrease in systemic vascular resistance predominated and the mean arterial pressure decreased, despite an increase in heart rate. From the time sequence it is likely that the

tachycardia was baroreflex mediated, although a direct myocardial or central effect can not be excluded. In view of the known effects of vasodilatation on peak aortic blood flow and acceleration, the increase in these variables does not necessarily imply an increase in myocardial contractility. Second, from about 2 min after injection, despite the less than normal systemic vascular resistance, heart rate and stroke volume decreased to less than baseline. These results are consistent with the findings that the baroreceptor reflex is "reset" at a smaller pressure value than normal by propofol [5]. The indices of left ventricular function were reduced, despite the continued decreased systemic vascular resistance; this may reflect either direct myocardial depression or a reduction in ventricular filling as a result of the peripheral vasodilatation.

These results help to explain differences found between previous studies. Propofol appears to affect the cardiovascular system in a biphasic manner. First, there is a marked reduction in systemic vascular resistance with an associated tachycardia, an increase in cardiac output and a decrease in arterial pressure. Second, the systemic vascular resistance increases towards normal, there is a decrease in heart rate and cardiac output, and a further decrease in arterial pressure.

REFERENCES

1. Lepage JM, Pinaud ML, Hélias JH, Juge CM, Cozian AY, Farinotti R, Souron R. Left ventricular function during propofol and fentanyl anesthesia in patients with coronary artery disease: Assessment with a radionuclide approach. *Anesthesia and Analgesia* 1988; 67: 949-955.
2. Lipman M, Paicuis R, Gingerich S, Owens R, Mok MS, Charney J, Lee TS, Harley D, Verespej J, Appel P. A controlled study of the hemodynamic effects of propofol *vs* thiopental during anesthesia induction. *Anesthesia and Analgesia* 1986; 65: S89.
3. Grounds RM, Twigley AJ, Carli JG, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. *Anaesthesia* 1985; 40: 735-740.
4. Vieli A. Doppler flow determination. *British Journal of Anaesthesia* 1988; 60: 107S-112S.
5. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans. *Anesthesia and Analgesia* 1987; 66: 1115-1120.

INVERSE CORRELATION BETWEEN THE PEAK VENOUS SERUM CONCENTRATION OF BUPIVACAINE AND THE WEIGHT OF THE PATIENT DURING INTERSCALENE BRACHIAL PLEXUS BLOCK

K. K. PIHLAJAMÄKI

SUMMARY

Thirty-five adult patients with rheumatoid arthritis received for 36 interscalene brachial plexus blocks a standard dose of bupivacaine 200 mg, regardless of the weight (range 39.2–102.5 kg) of the patient. The peak venous serum concentrations (C_{max}) of bupivacaine, measured by HPLC, were in the range 0.82–4.30 mg litre⁻¹; there were no signs of toxicity. There was a very significant inverse correlation between the C_{max} of bupivacaine and the weight of the patient ($r = -0.5922$; $t = -4.285$; $P = 0.0001$, Pearson's test). In spite of the correlation, only 35.1% of the total variance could be explained by regression. Thus weight had little influence on C_{max} under interscalene brachial plexus block.

KEY WORDS

Anaesthetics, local: bupivacaine. Anaesthetic techniques: interscalene brachial plexus block. Pharmacokinetics: age factors.

For upper extremity orthopaedic surgery, for many years we have successfully used interscalene brachial plexus block [1] with 0.5% plain bupivacaine hydrochloride 40 ml, as this volume produces a greater area of block than 30 ml [2]. In many countries, a maximal recommended dose of bupivacaine 2 mg/kg body weight is recommended. However, no correlation between the peak venous serum concentration (C_{max}) of the local anaesthetic agent and the weight of the patient has been found during interscalene brachial plexus block. The aim of the present study was to determine if a correlation could be obtained using a standard dose of bupivacaine 200 mg.

METHODS AND RESULTS

We studied 36 interscalene brachial plexus blocks in 35 adult patients (24 women and 11 men), undergoing orthopaedic surgery on an upper limb because of active rheumatoid arthritis. One man (in group 1) participated twice. All the patients gave informed consent for the study, which was approved by the local Ethics Committee.

In group 1 ($n = 25$), patients received 0.5% plain bupivacaine 40 ml; group 2 patients ($n = 11$) received the same volume of 0.5% bupivacaine mixed with physiological saline 20 ml. In group 1, the mean age was 54 yr (range 28–81 yr), the mean weight 65 kg (39.2–102.5 kg) and the mean height 163 cm (143–181 cm); respective values for group 2 were 56 yr (30–72 yr), 65 kg (47–85 kg) and 164 cm (148–185 cm).

Diazepam 10 mg was given orally on the preceding evening and on the morning of the day of operation for premedication. After the block was completed according to Winnie [1], the injected solution was massaged thoroughly down the neck. All the patients had a tourniquet above the elbow. Separate blocks of the intercosto-brachial and medial brachial cutaneous nerves were not performed. Heart rate and systolic and diastolic arterial pressures were measured every 5 min until the end of surgery.

Blood samples for measurement of venous serum concentrations of bupivacaine were ob-

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tained at 0, 10, 20, 30, 40, 50, 60, 90 and 120 min from a venous cannula in the contralateral arm. The sera were separated and stored at -20°C until assayed by HPLC [3]. The limit of detection of bupivacaine was $0.02\text{ mg litre}^{-1}$, the coefficient of variation for intra-assay variability 2.1% and that for inter-assay variability, 5.7%.

Statistical comparisons of circulatory variables and serum concentration curves of bupivacaine between the two groups were carried out using ANOVA. The least squares method of regression was used and the significance of the correlation was analysed by Pearson's test. $P \leq 0.05$ was considered significant.

The venous serum concentration curve of bupivacaine was identical in both groups. In group 1, C_{max} of bupivacaine was 2.26 (SD 0.85) mg litre^{-1} (range 0.82 – $4.30\text{ mg litre}^{-1}$), and the median time after administration of bupivacaine to peak serum concentration (tC_{max}) was 29.6 min (95% confidence limits (CL) 20–30 min, range 10–60 min). In group 2, C_{max} was 2.23 (SD 0.70) mg litre^{-1} (range 1.44 – $3.54\text{ mg litre}^{-1}$), and tC_{max} 30.3 min (range 10–60 min). In figure 1, a plot of the peak venous serum concentration of bupivacaine against the weight of the patient is shown. Median C_{max} was $2.11\text{ mg litre}^{-1}$, 5.0 percentile $1.02\text{ mg litre}^{-1}$ and 95.0 percentile $3.88\text{ mg litre}^{-1}$. For the least squares regression line, the intercept was 4.82 (95% CL 3.62 – 6.01) and the slope -0.039 ± 0.009 (95% CL -0.057 and -0.020). By Pearson's test $r = -0.5922$, $t = -4.285$ and $P = 0.0001$.

COMMENT

In a previous study, after using 0.5% bupivacaine 30 ml without adrenaline for the brachial plexus block, it was found that C_{max} was 2.2 mg litre^{-1} [4], equal to that obtained in the present study with 40 ml of 0.5% bupivacaine. An increase in volume, but not dose, of bupivacaine in the present study had no effect on the circulation or on the time–concentration curve (C_{max} or tC_{max}) of bupivacaine, which is in agreement with previous studies [5]. There was a significant negative correlation between the C_{max} of bupivacaine and the weight of the patient. Because the

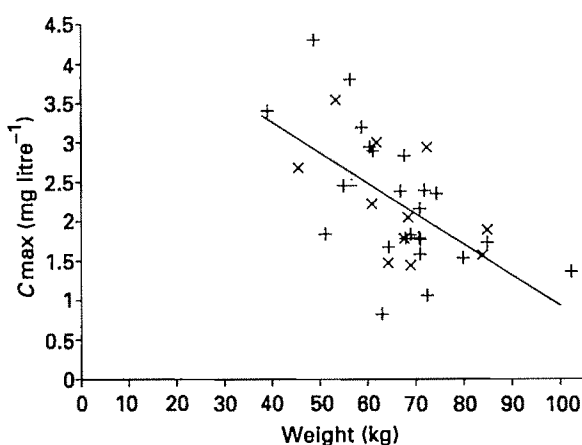


FIG. 1. Plot of the peak venous serum concentration of bupivacaine against the weight of the patient. + = Group 1 ($n = 25$); $\times$ = group 2 ($n = 11$). The least squares regression line from all 36 sessions is shown.

weight of the patients varied from 39.2 to 102.5 kg, the dose range of bupivacaine varied from 1.95 to 5.1 mg kg^{-1} . Although the venous serum concentration of bupivacaine often exceeded the estimated toxic threshold in man (2 mg litre^{-1}), there were no signs of toxicity. In spite of the correlation, only 35.1% of the total variance could be explained by regression ($r^2 = 0.3507$). Thus weight had little influence on C_{max} .

ACKNOWLEDGEMENT

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REFERENCES

1. Winnie AP. Interscalene perivascular technique of brachial plexus block. In: Häkansson L, ed. *Plexus Anesthesia*, Vol. I. Copenhagen: Schultz Medical Information ApS., 1983; 167.
2. Winnie AP, Radonjic R, Akkineni SR, Durrani Z. Factors influencing distribution of local anesthetic injected into the brachial plexus sheath. *Anesthesia and Analgesia* 1979; 58: 225–234.
3. Lindberg RLP, Pihlajamäki KK. High-performance liquid chromatographic determination of bupivacaine in human serum. *Journal of Chromatography* 1984; 309: 369–374.
4. Wildsmith JAW, Tucker GT, Cooper S, Scott DB, Covino BG. Plasma concentrations of local anaesthetics after interscalene brachial plexus block. *British Journal of Anaesthesia* 1977; 49: 461–466.
5. Tucker GT. Pharmacokinetics of local anaesthetics. *British Journal of Anaesthesia* 1986; 58: 717–731.

RESISTANCE TO ATRACURIUM IN A PATIENT WITH AN INCREASE IN PLASMA ALPHA₁ GLOBULINS†

A. J. TATMAN, S. R. WRIGLEY AND R. M. JONES

SUMMARY

We observed that a female patient with a poorly differentiated adenocarcinoma of the stomach undergoing gastrectomy was markedly resistant to the action of the neuromuscular blocking drug atracurium. There was no evidence of tumour metastasis and her liver function tests were normal. Electrophoresis of plasma proteins revealed a marked increase in alpha₁ globulin. Alpha₁ acid glycoprotein is an acute phase reactant that is increased in patients with cancer and is present in the alpha₁ globulin electrophoresis pattern. It is likely that the mechanism for the resistance to neuromuscular block in the patient was an increase in drug binding to alpha₁ acid glycoprotein.

KEY WORDS

Neuromuscular relaxants: atracurium. Complications: drug resistance. Protein: alpha₁ globulins.

with liver disease [14-18]. We report the case history of a patient who was markedly resistant to the action of atracurium, in the absence of manifest hepatic disease, but who did have a documented increase in alpha₁ globulins.

CASE REPORT

A 65-year-old woman presented to the surgical outpatient department with a 5-month history of weight loss and, more recently, dysphagia and abdominal pain. Before this episode, she had been well and the only relevant previous history was that she had undergone a total abdominal hysterectomy in 1975. She was not receiving any regular medication.

The patient underwent gastroscopy, and mucosal biopsy revealed a poorly differentiated adenocarcinoma. She was admitted to hospital for gastrectomy where preoperative investigations revealed a normochromic, normocytic anaemia (haemoglobin 10.3 g dl⁻¹) and a neutrophil leucocytosis (white cell count 13.2 × 10⁹ litre⁻¹). Plasma electrolytes and corrected serum calcium concentrations were within the normal range. Her liver function tests also were normal: alkaline phosphatase 206 iu litre⁻¹ (normal value < 300 iu litre⁻¹), total bilirubin 4 µmol litre⁻¹ (< 23 µmol litre⁻¹), aspartate transaminase 11 iu litre⁻¹ (< 43 iu litre⁻¹). Total globulins were 28 g litre⁻¹; immunoglobulins were: IgG 12.8 g litre⁻¹ (9-18.5 g litre⁻¹), IgA 2.3 g litre⁻¹ (0.8-4.6 g litre⁻¹), IgM 1.1 g litre⁻¹ (0.4-3.0 g litre⁻¹).

This article is accompanied by Editorial 1.

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†The case reported in this manuscript was undertaken at Guy's Hospital, London SE1.

Several factors are known to cause resistance to the action of non-depolarizing neuromuscular blocking drugs. These include a variety of neurological conditions such as upper motor neurone lesions [1, 2], multiple sclerosis [3] and disuse atrophy [4] in addition to non-neurological conditions such as thermal injury [5-7] and concomitant administration of anticonvulsant drugs [8-10]. It has also been known since 1953 that patients with liver disease may be resistant to the action of tubocurarine [11] and, since that time, several reports have appeared which indicate that this occurs also with other drugs such as pancuronium [12, 13] and atracurium [14]. It is likely that the underlying cause of resistance differs according to the specific condition and blocking agent in question, but there have been conflicting reports on the role of altered plasma proteins, especially in burns patients [7] and those

Electrophoresis revealed a marked increase in α_1 globulins. Plasma concentration of albumin was 19 g litre^{-1} ($30\text{--}46 \text{ g litre}^{-1}$). Abdominal ultrasound revealed normal liver, kidneys and spleen, with no evidence of metastases. The patient's preoperative weight was 70.5 kg and the body mass index 29.8.

The patient was premedicated with temazepam 20 mg and anaesthesia was induced using a rapid sequence technique with thiopentone 3.5 mg kg^{-1} and suxamethonium 1.3 mg kg^{-1} . Anaesthesia was maintained with 66% nitrous oxide and 0.5–1.0% isoflurane in oxygen with an initial dose of alfentanil $30 \mu\text{g kg}^{-1}$ followed by increments of $15 \mu\text{g kg}^{-1}$. Following return of neuromuscular transmission (determined by train-of-four stimulation of the ulnar nerve), atracurium 25 mg (0.35 mg kg^{-1}) was administered which had no influence on the train-of-four. An additional 20 mg was given, which had the effect of reducing the fourth twitch in the train, but the patient was still clinically not paralysed. A different batch of atracurium was obtained fresh from the refrigerator and an additional 25 mg was given, which resulted in the abolition of the second, third and fourth twitches but not the first. After 30 min the train-of-four ratio had returned to normal and an additional 40 mg of atracurium resulted in abolition of the third and fourth twitches only. The procedure took approximately 70 min, after which the administration of neostigmine 2.5 mg caused prompt antagonism of block, with full return of the train-of-four response. Subsequently, the patient made an uneventful recovery with no signs of recurarization. Perioperative drugs included alfentanil, cefuroxime and metronidazole; the patient remained haemodynamically stable throughout the procedure. At operation there was evidence of local lymph node and omental involvement, but the liver and spleen were clear of tumour. In the immediate post-operative period the patient's temperature was 36.5°C .

DISCUSSION

Dundee and Gray first commented in 1953 on the resistance to tubocurarine that may occur in the presence of liver disease [11]. Subsequent reports came to conflicting conclusions on the role of increased binding to plasma proteins and whether or not the protein subfraction involved was albumin or gamma globulin [15–18]. Soon after the introduction of pancuronium into clinical

practice, reports appeared indicating that there was resistance also to this drug in patients with liver disease [12, 13]. The liver plays an important role in the disposition of pancuronium, and it was reported that the resistance was caused by an increase in distribution and elimination half-life and a decrease in clearance [19, 20]. In contrast to its involvement in the disposition of pancuronium, the liver does not play an important role in the disposition of atracurium. However, as Gyasi and Naguib have reported recently, severe liver disease may be associated also with resistance to atracurium [14]. An alteration in plasma binding can influence the pharmacological activity of a drug, and in general a decrease in volume of distribution and a shortening of half-life occur [21, 22]. This would result in an increase in drug requirement for any given effect. Unlike acidic drugs, which are bound largely to albumin, basic drugs—although binding to some extent to albumin—associate more avidly with other plasma proteins [23]. The principal proteins to which basic drugs are bound include lipoproteins and α_1 acid glycoprotein [24]. Both these are present in the α_1 globulin fraction determined by electrophoresis. The varying results reported for the binding of neuromuscular blockers to gamma globulin have been referred to previously but it appears that, in general, basic drugs are not bound significantly to this fraction [24]. Of the two fractions associated with α_1 globulin, α_1 acid glycoprotein appears to play the major role in increasing binding in disease states [23, 24]. This acute phase reactant is known to increase non-specifically in response to a large number of conditions characterized by physiological stress such as infection, inflammation, trauma and, as in our report, cancer [25]. Although electrophoresis in our laboratory is unable to distinguish between the subfractions of α_1 globulin, in view of the association between carcinoma and the acute phase reactant, α_1 acid glycoprotein, we suggest that increased binding of atracurium to this plasma protein is the most likely explanation for the marked increase in dose requirement observed in our patient. In these circumstances it is probable that the decrease in albumin concentration had little or no influence on the overall binding of atracurium and was therefore largely an incidental finding.

It is widely appreciated that there is great individual variation in response to neuromuscular blocking drugs, but we believe that the degree of

resistance exhibited by our patient was such that it is highly unlikely that her response was merely that of a normal but insensitive individual. Another observation reinforces our point of view. The notes of her previous operation were available and revealed that, during her previous anaesthetic (for hysterectomy), she was given a total of 160 mg of gallamine for the procedure, which lasted 60 min.

In conclusion, we suggest that increased binding of atracurium to α_1 globulin plasma proteins was the most likely cause of resistance in our patient. α_1 acid glycoprotein is an acute phase reactant that is increased in patients with cancer and is present in the α_1 globulin electrophoretic fraction. An increase in this fraction is known to cause an increase in binding of basic drugs, which in turn leads to an increase in dose requirement for any given effect. It seems possible that this was the specific mechanism for resistance in our patient and, because of the variety of conditions, including thermal injury, that can lead to an increase in concentrations of α_1 acid glycoprotein, this may be the underlying cause in several circumstances.

REFERENCES

1. Graham DH. Monitoring neuromuscular block may be unreliable in patients with upper-motor-neuron lesions. *Anesthesiology* 1980; 52: 74-75.
2. Moorthy SS, Hilgenberg JC. Resistance to non-depolarizing muscle relaxants in paretic upper extremities of patients with residual hemiplegia. *Anesthesia and Analgesia* 1980; 59: 624-627.
3. Brett RS, Schmidt JH, Gage JS, Schartel DO, Poppers PJ. Measurement of acetylcholine receptor concentration in skeletal muscle from a patient with multiple sclerosis and resistance to atracurium. *Anesthesiology* 1987; 66: 837-839.
4. Gronert GA. Disuse atrophy with resistance to pancuronium. *Anesthesiology* 1981; 55: 547-549.
5. Martyn JAJ, Szyfelbein SK, Ali HA, Matteo RS, Savarese JJ. Increased d-tubocurarine requirement following major thermal injury. *Anesthesiology* 1980; 52: 352-355.
6. Dwersteg JF, Pavlin EG, Heimbach DM. Patients with burns are resistant to atracurium. *Anesthesiology* 1986; 65: 516-517.
7. Pavlin EG, Haschke RH, Karnik P, Zucker JR, Slattery JT, Howard ML. Resistance to atracurium in thermally injured rats. *Anesthesiology* 1986; 65: A113.
8. Ornstein E, Matteo RS, Schwartz AE, Silverberg PA, Young WL, Diaz J. The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. *Anesthesiology* 1987; 67: 191-196.
9. Modica P, Tempelhoff R. Effect of chronic anticonvulsant therapy on recovery from atracurium. *Anesthesia and Analgesia* 1989; 68: S198.
10. Desai P, Hewitt PB, Jones RM. Influence of anticonvulsant therapy on doxacurium and pancuronium-induced paralysis. *Anesthesiology* 1989; 71: A276.
11. Dundee JW, Gray TC. Resistance to d-tubocurarine chloride in the presence of liver damage. *Lancet* 1953; 2: 16-17.
12. Nana A, Cardan E, Leitersdorfer T. Pancuronium bromide: its use in asthmatics and patients with liver disease. *Anaesthesia* 1972; 27: 154-158.
13. Ward ME, Adu-Gyamfi Y, Strunin L. Althesin and pancuronium in chronic liver disease. *British Journal of Anaesthesia* 1975; 47: 1199-1204.
14. Gyasi HK, Naguib M. Atracurium and severe hepatic disease: a case report. *Canadian Anaesthetists Society Journal* 1985; 32: 161-164.
15. Aladjemoff L, Dilestein S, Shafir B. Binding of d-tubocurarine to plasma proteins. *Journal of Pharmacology and Experimental Therapeutics* 1958; 123: 43-48.
16. Baraka A, Gabali F. Correlation between tubocurarine requirements and plasma protein pattern. *British Journal of Anaesthesia* 1968; 40: 89-93.
17. Ghoneim MM, Kramer B, Bannow R, Pandya H, Routh JJ. Binding of d-tubocurarine to plasma proteins in normal man and patients with hepatic or renal disease. *Anesthesiology* 1973; 39: 410-415.
18. Stovner J, Theodorsen L, Bjelke E. Sensitivity to gallamine and pancuronium with special reference to serum proteins. *British Journal of Anaesthesia* 1971; 43: 953-958.
19. Duvaldestin P, Agostson S, Henzel D, Kersten UW, Desmonts JM. Pancuronium pharmacokinetics in patients with liver cirrhosis. *British Journal of Anaesthesia* 1978; 50: 1131-1136.
20. Somogyi AA, Shanks CA, Triggs EJ. Disposition kinetics of pancuronium bromide in patients with total biliary obstruction. *British Journal of Anaesthesia* 1977; 49: 1103-1108.
21. Wilkinson GR, Shand DG. A physiological approach to hepatic drug clearance. *Clinical Pharmacology and Therapeutics* 1975; 18: 377-390.
22. Evans GH, Neis AS, Shand DG. The disposition of propranolol III. Decreased half-life and volume of distribution as a result of plasma binding in man, monkey, dog and rat. *Journal of Pharmacology and Experimental Therapeutics* 1973; 186: 114-122.
23. Pfafsky KM. Disease-induced changes in the plasma binding of basic drugs. *Clinical Pharmacokinetics* 1980; 5: 246-262.
24. Pfafsky KM, Borga O, Odar-Cederlof I, Johansson C, Sjoqvist F. Increased plasma protein binding of propranolol and chlorpromazine mediated by disease induced elevation of plasma α_1 -acid glycoprotein. *New England Journal of Medicine* 1978; 299: 1435-1439.
25. Schmid K. α_1 -acid glycoprotein. In: Putnam FW, ed. *The Plasma Proteins* Vol. I. New York: Academic Press, 1975; 183-228.

POSTOPERATIVE MYOCARDIAL ISCHAEMIA: TEMPORAL ASSOCIATION WITH NOCTURNAL HYPOXAEMIA

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SUMMARY

Three patients presenting for elective aortic surgery were studied before operation and for up to 3 days after operation with ambulatory electrocardiographic monitoring and nocturnal pulse oximetry. Supplementary oxygen was administered for the first 2 days after operation and withdrawn on the 3rd morning after operation. Heart rate remained increased for the first 3 days after operation. Two patients developed episodes of myocardial ischaemia during the first 48 h after operation while their arterial oxygen saturation remained greater than 90%. On the third day, and during the third night after operation, both the severity and duration of myocardial ischaemia increased markedly, associated with arterial hypoxaemia. A temporal relationship between decreases in oxygen saturation and fluctuations in ST segment level were observed in the three patients.

KEY WORDS

Heart: ischaemia. Hypoxaemia. Surgery: vascular.

We have reported previously that ischaemic ST depression during preoperative ambulatory electrocardiographic monitoring occurs in approximately 20% of patients presenting for vascular surgery [1]. They are thus a group potentially at risk from myocardial ischaemia in the postoperative period. Whilst pursuing a study of the incidence of silent ischaemia in the pre- and postoperative periods, we noted three patients who developed marked ST depression in association with episodes of oxygen desaturation during sleep in the postoperative period. We present these case reports to emphasize the importance of postoperative oxygen therapy and

to increase awareness of the potential hazards of respiratory disturbances which occur during sleep in the late postoperative period.

After informed verbal consent, we studied three patients undergoing elective aortic reconstructive surgery with ambulatory ECG monitoring before surgery and for the first 3 days after surgery. In addition, continuous pulse oximetry measurements were obtained on the night before surgery and overnight for the first three nights after operation, in order to observe possible temporal relationships between episodes of hypoxaemia and the development of myocardial ischaemia.

All patients had been investigated with a detailed medical history, physical examination and routine preoperative tests including full blood count, serum urea and electrolyte concentrations, chest radiograph and 12-lead electrocardiograph. In one patient, independent evaluation of myocardial function was made using a radionuclide gated heart blood pool scan (MUGA). No patient was considered to have an increased cardiovascular risk for the type of surgery.

METHODS

Preoperative monitoring

ECG recordings were made using the solid state Oxford Medilog 6000 FD recording system attached to two bipolar electrodes. Electrodes were placed to record from an inferior (lead 2) and

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a precordial (CM5) lead. Patients were monitored for 15–21 h before operation and were exposed to normal preoperative ward routine during the monitoring.

Arterial oxygen saturation (Sp_{O_2}) and heart rate were sampled once each 1 s from the digital output of an oximeter (Ohmeda 3700) by a portable microcomputer at the bedside from 21:00 until removal of the finger probe just before surgery. Oximetry data were stored in consecutive 30-min files. Precise timing of hypoxaemic events and synchronization with ECG recordings was achieved by setting the time on the computer at the start of oximetry monitoring to correspond to that on the ECG monitoring system.

Postoperative monitoring

Ambulatory ECG monitoring was resumed immediately after surgery in the intensive care unit, and continued until the morning of the 4th day after operation in two of the patients. In the third patient the onset of renal failure required hospital transfer on the third day after operation and monitoring was possible only up to the 3rd morning after operation. Nocturnal oximetry recordings were performed overnight on the first three nights after operation. We elected not to perform continuous oximetry monitoring during the daytime in order to improve patient compliance for overnight oximetry. However, during the first two days nurses paid close attention to maintaining the continuity of the patient's oxygen therapy. We have observed previously that supervised oxygen therapy is almost 100% effective in preventing hypoxaemia ($< 90\% Sa_{O_2}$) in vascular patients during this period.

Data analysis

Recorded ECG data were analysed using software (Oxford Medilog 6000) on a computer and all ST segment changes reported by the computer were checked by one of the investigators. Significant ST segment depression was defined by the following criteria: planar or downsloping ST segments, shifted 1 mm or more below baseline, which persisted for more than 60 ms after the J point and appearing in consecutive beats lasting for more than 60 s. Each episode was terminated by a return of ST segment to within 1 mm of baseline. For each episode of ST segment depression, the duration of the episode was noted.

Pulse oximetry data were replayed so that significant changes in Sp_{O_2} could be identified

visually and analysed manually to determine their nature. Overall oxygenation was determined using a computer program designed for respiratory sleep studies and values for the overnight mean Sp_{O_2} and the least 30-min mean epoch were obtained. Synchrony of ECG recorders and oximeters to within a few seconds of each other allowed plots of heart rate, Sp_{O_2} and simultaneous ECG to be made.

Perioperative management

Patients continued to receive their normal cardiac medication before operation but it was discontinued during the postoperative period of monitoring. All patients received a standard general anaesthetic technique. Premedication was provided by papaveretum and hyoscine and anaesthesia was induced with thiopentone and fentanyl. Anaesthesia was maintained with a volatile agent and 70% nitrous oxide in oxygen. Routine postoperative care of patients undergoing aortic surgery was not altered during the conduct of this study. Patients received supplementary oxygen 4–6 litre min^{-1} via a Hudson mask for the first two days after operation and were given i.m. or i.v. opioids for pain relief for the duration of the study. Fluid replacement was monitored using clinical observation and hourly urine output, aided by central venous pressure monitoring (CVP). No patient was monitored with a pulmonary artery catheter.

CASE REPORTS

Patient No. 1

A 66-yr-old man presented for elective repair of an aortic aneurysm. He had a past history of hypertension and had suffered a myocardial infarction 2 years previously. His hypertension was controlled using atenolol and he remained free from angina.

Patient No. 2

A 67-yr-old man with claudication presented for an aorto-bifemoral graft. He gave a past history of diabetes mellitus, treated by diet alone, and hypertension controlled by diuretic therapy.

Patient No. 3

A 68-yr-old man presented for elective repair of an aortic aneurysm. He had suffered two previous myocardial infarctions, the second in 1989, and

TABLE I. Sp_{O_2} , heart rate and duration of silent ischaemia for the day before and first 3 days after operation. † Onset of renal failure prevented further study on day 3. * Total—patient developed ischaemia only, while $Sp_{O_2} < 85\%$

	Postoperative day			
	Pre-op.	1	2	3
Patient No. 1				
Mean Sp_{O_2} (%)				
Nocturnal	93.5	96.8	92	68.7
Least 30-min	92.6	93	90.7	56.4
Silent ischaemia (min h^{-1})				
During study	0	30	7	43
Nocturnal (21:00–09:00)	—	12	11	48
Heart rate (beat min^{-1})				
Mean	72	85	90	100
Maximum	85	105	108	122
Patient No. 2†				
Mean Sp_{O_2} (%)				
Nocturnal	93.9	96	—	—
Least 30-min	92.7	88	—	—
Silent ischaemia (min)*	0	11*	0	—
Heart rate (beat min^{-1})				
Mean	74	104	100	—
Maximum	92	125	120	—
Patient No. 3				
Mean Sp_{O_2} (%)				
Nocturnal	94.6	99.5	98.1	89
Least 30-min	93.5	98	97	87
Silent ischaemia (min h^{-1})				
During study	1	10	9	50
Nocturnal (21:00–09:00)	—	0	10	33
Heart rate (beat min^{-1})				
Mean	53	100	103	103
Maximum	128	125	125	132

continued to suffer from mild angina in the early mornings. Treatment consisted of diltiazem and isosorbide dinitrate. ECG showed signs of an old infero-lateral myocardial infarction and radio-nuclide gated heart blood pool scan (MUGA) demonstrated posterior hypokinesia with a resting ejection fraction of 53%.

Postoperative course

Table I shows for each patient, the pre- and postoperative values of oxygen saturation (mean overnight and least 30-min mean Sp_{O_2}), heart rate (mean and maximum values), and duration of silent ischaemia.

Heart rate was increased immediately after operation and reached a plateau on the 2nd or 3rd day after operation (patients Nos 1 and 3) (table I). Tachycardia began to subside during the course of the 4th day after operation.

Administration of supplementary oxygen maintained mean overnight oxygen saturations above or close to preoperative values for the first 2 days

after operation. Discontinuation of oxygen therapy in patients Nos 1 and 3 on the third morning after operation resulted in severe hypoxaemia with patient No. 1 spending his whole night with a mean Sp_{O_2} of 68.7%. Patient No. 2 refused to continue with oximetry monitoring on night two. However, he continued to receive supplementary oxygen during his 2nd day and night after operation.

Only patient No. 3 showed any preoperative evidence of silent ischaemia, developing 2–3 mm of ST depression at 07:00 on the morning of surgery. Myocardial ischaemia increased significantly in the postoperative period. Patients Nos 1 and 3 suffered periods of myocardial ischaemia during their first 2 days after operation; however in both patients, the amount of ischaemia increased notably during their 3rd day and night after operation. The ischaemia observed during the 3rd night after operation was more severe compared with previous nights, with frequent episodes of ST depression to between –2 and –5

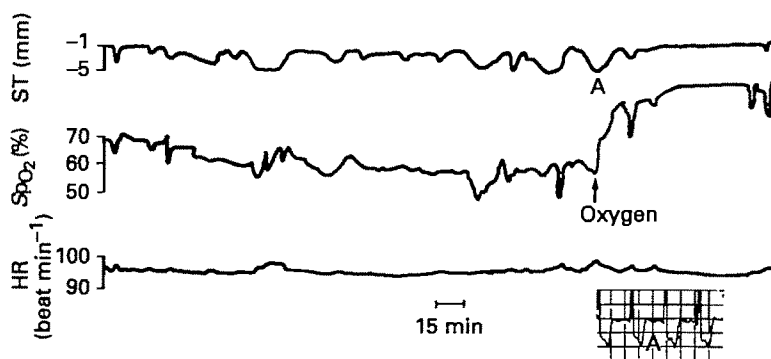


FIG. 1. Patient No. 1: ST segment level, saturation and heart rate (HR) plotted during the third night after operation. Oxygen was administered after the patient was noted to be hypoxaemic. Fluctuations in ST segment are closely related to reductions in Sp_{O_2} . Administration of oxygen stabilized ST baseline until the oxygen was withdrawn in the morning.

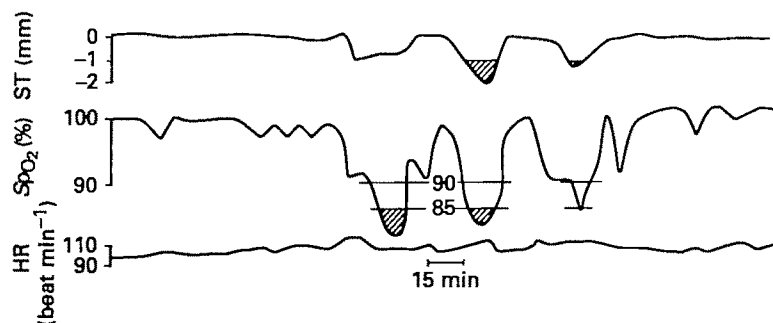


FIG. 2. Patient No. 2: ST segment level, saturation and heart rate (HR) plotted during the first night after operation. Removal of oxygen was associated with severe decreases in Sp_{O_2} and periods of ischaemia. No ischaemic episode occurred while the patient received oxygen.

mm. Patient No. 2 developed a total of 11 min of ischaemia during the first night after operation.

Temporal association of hypoxaemia with the development of ST segment depression

Patient No. 1. There was a close association between changes in heart rate and reductions in Sp_{O_2} (fig. 1). The patient's mean saturation for the whole night was 68.7% and the patient was severely ischaemic. Fluctuations in oxygen saturation matched closely further depression of the ST segment. Administration of oxygen abolished the fluctuations in ST until oxygen was removed in the early morning, when ST fluctuations were observed to return.

Patient No. 2. Figure 2 shows simultaneous plots of Sp_{O_2} , heart rate and ST segment during part of his first night after operation on the ward.

During the night, his oxygen mask was displaced on three occasions, resulting in Sp_{O_2} decreasing to less than 85%. These severe reductions in Sp_{O_2} were associated with significant ST segment depression. With supplementary oxygen, no further fluctuations in ST segment were observed for the remainder of the night, despite periodic increases in heart rate equal to those shown in the figure. Removal of oxygen in the early morning resulted in a further desaturation to less than 85% and a synchronous episode of ST segment depression.

Patient No. 3. Episodic decreases in Sp_{O_2} and increases in heart rate were associated with nocturnal respiratory irregularity. Worsening saturation (Sp_{O_2} 85%) immediately preceded increases in severity of myocardial ischaemia during the patient's third night after operation.

Oxygen therapy was re-instituted and there were no further ST segment fluctuations during the remainder of the night.

DISCUSSION

Increases in heart rate are believed to be important in precipitating myocardial ischaemia but, in the majority of cases, preoperative myocardial ischaemia is not preceded by increases in mean heart rate greater than 20% [1]. Other reports of patients with angina have found myocardial ischaemia associated with increases in heart rate [2], but this finding is not uniform [3–10]. It may be expected, however, that factors resulting in an increase in heart rate may promote an increase in duration and severity of ischaemia in susceptible individuals in the postoperative period.

In the patients described, postoperative tachycardia was a persistent phenomenon. After anaesthesia and surgery, heart rate increased and reached a plateau during the 2nd and 3rd days after operation. During the 4th day, heart rate began to decrease. During the first two nights after operation, periods of myocardial ischaemia occurred at increased heart rates, while oxygen saturation remained satisfactory because of supplementary oxygen.

In most centres, prescription of supplementary oxygen is usually discontinued before or by the 3rd day after operation unless there are clinical indications that it should continue. As a result of this practice, patient No. 3 and especially patient No. 1, were exposed to prolonged periods of severe hypoxaemia which were not detected clinically. One factor in the equation determining the balance between myocardial oxygen supply and demand is arterial oxygenation. On the 3rd day after operation there was a large decrease in the mean overnight saturation values and also therefore the least 30-min mean values. In addition, there was a large increase in both the duration and severity of the observed ischaemia, at heart rates essentially unchanged (especially patient No. 1) from the 2nd day after operation. In view of the observed temporal association between hypoxaemia and the development or worsening of myocardial ischaemia, we agree with Rosenberg and co-workers [11] that these patients demonstrate that hypoxaemia is a participating factor in the development of postoperative myocardial ischaemia. Almost half a century ago, experimental reductions in inspired oxygen, pro-

ducing Sp_{O_2} values between 60 and 85%, were frequently associated with chest pain in patients with ischaemic heart disease [12].

Mangano and colleagues [13] recently studied the association between transient postoperative myocardial ischaemia and cardiac morbidity and mortality in men undergoing non-cardiac surgery. They found that early postoperative myocardial ischaemia correlated well with risk of an adverse cardiac outcome such as myocardial infarction (fatal or non-fatal), angina, cardiac failure and ventricular tachycardia. Pasternack and colleagues [14] noted that the sole predictor of postoperative myocardial infarction was the presence of perioperative myocardial ischaemia, whether silent or symptomatic. It is possible that the combination of an increased heart rate and decreased oxygen saturation may account in part for the observed increase in incidence of myocardial infarction on the third day after operation reported by Rao, Jacobs and El-Etr [15]. None of our patients was investigated for the presence of new postoperative myocardial damage, although after night 3, patient No. 1 developed persistent ECG changes suggestive of severe subendocardial ischaemia or infarction. Apart from myocardial infarction, repetitive ischaemic insults, insufficient to cause myocyte death, have been associated with marked impairment in cardiac performance [16]. This concept of the "stunned myocardium", with a delayed return to full ventricular myocardial function, would appear to be relevant to the postoperative period after aortic surgery. Transient ischaemic episodes are common during this period, and may contribute to impairment of myocardial function. Close monitoring of haemodynamic fluctuations, oxygen saturation and the maintenance of oxygen therapy for at least the first 3 days after operation, would appear useful in an attempt to protect patients from myocardial ischaemia after major abdominal vascular surgery. This may be difficult to achieve, except in a high-dependency environment. It is also of interest that none of our patients continued with their normal cardiac medications in the early postoperative period. The significance of this in the development of postoperative ischaemia needs to be examined.

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REFERENCES

1. Muir AD, Reeder M, Foëx P, Ormerod OJM, Sear JW, Johnson C. Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population. *British Journal of Anaesthesia* 1991; 67: 373-377.
2. Quyyumi AA, Efthimiou J, Quyyumi A, Mockus LJ, Spiro SG, Fox KM. Nocturnal angina: precipitating factors in patients with coronary artery disease and those with variant angina. *British Heart Journal* 1986; 56: 346-352.
3. Deanfield JE, Maseri A, Selwyn AP, Ribeiro P, Chierchia S, Krikler S, Morgan M. Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. *Lancet* 1983; 2: 753-758.
4. Wong MG, Wellington YC, London MJ, Layug E, Li J, Mangano DT. Prolonged postoperative ischemia in high-risk patients undergoing non-cardiac surgery. *Anesthesiology* 1988; 69: A56.
5. Raby KE, Goldman L, Creager MA, Cook SE, Weisberg MC, Whittemore AD, Selwyn AP. Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. *New England Journal of Medicine* 1989; 321: 1296-1300.
6. McIntyre RW, Baldwin B, Smith LR. The relationship between heart rate and myocardial ischemia in noncardiac surgical patients. *Anesthesia and Analgesia* 1989; 68: S192.
7. Clements FM, Kok S, de Kok E, McCann R. Perioperative ischemia: should we be less tolerant of tachycardia? *Anesthesiology* 1988; 69: A50.
8. Fegert G, Hollenberg M, Browner W, Wellington Y, Levenson L, Franks M, Harris D, Mangano D. Perioperative myocardial ischemia in the noncardiac surgical patient. *Anesthesiology* 1988; 69: A49.
9. Knight AA, Hollenberg M, London MJ, Tubau J, Verrier E, Browner W, Mangano DT. Perioperative myocardial ischemia: are anesthesia and surgery truly stressful to the ischemic heart? *Anesthesiology* 1987; 67: A592.
10. Knight AA, Hollenberg M, London MJ, Tubau J, Verrier E, Browner W, Mangano DT. Perioperative myocardial ischemia: Importance of preoperative ischemic pattern. *Anesthesiology* 1988; 68: 681-688.
11. Rosenberg J, Rasmussen V, van Jensen F, Ullstad T, Kehlet H. Late postoperative episodic and constant hypoxaemia and associated ECG abnormalities. *British Journal of Anaesthesia* 1990; 65: 684-691.
12. Barach AL, Steiner A, Eckman M, Molomut N. The physiologic action of oxygen and carbon dioxide on the coronary circulation, as shown by blood gas and electrocardiographic studies. *American Heart Journal* 1941; 22: 13-34.
13. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. *New England Journal of Medicine* 1990; 323: 1781-1787.
14. Pasternack PF, Grossi EA, Baumann FG, Riles TS, Lamparello PJ, Giangolla G, Primus LK, Mintzer R, Imparato AM. The value of silent myocardial ischemia monitoring in the prediction of perioperative myocardial infarction in patients undergoing peripheral vascular surgery. *Journal of Vascular Surgery* 1989; 10: 617-625.
15. Rao TLK, Jacobs KHJ, El-Etr AA. Reinfarction following in anesthesia in patients with myocardial infarction. *Anesthesiology* 1983; 59: 499-505.
16. Braunwald E, Kloner RA. The stunned myocardium: prolonged postischemic ventricular dysfunction. *Circulation* 1982; 66: 1146-1149.

UNUSUAL PRESENTATION OF ACUTE UPPER AIRWAY OBSTRUCTION CAUSED BY AN ANTERIOR MEDIASTINAL MASS

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SUMMARY

We report an unusual case of acute upper airway obstruction. Inhalation of a foreign body caused choking in a 5-yr-old child, but subsequent investigations revealed a large anterior mediastinal tumour, externally compressing the trachea and the main bronchi. Such a presentation may be deceptive and is important, as general anaesthesia may result in complete airway obstruction with fatal consequences.

KEY WORDS

Airway: acute obstruction, mediastinal tumour.

Acute airway obstruction is a serious emergency. Infections and inhalation of foreign bodies comprise the majority of such cases in children, who may be confidently diagnosed by clinical history and examination. General anaesthesia may be required either for tracheal intubation to bypass the obstruction or to remove the foreign body. A less common cause in children is compression of trachea and bronchi by mediastinal tumours. Up to 60% of children with mediastinal masses may present with respiratory symptoms [1]. General anaesthesia in these patients is contraindicated, as relaxation of the tracheal musculature may cause collapse and complete obstruction, with fatal consequences.

CASE REPORT

A 5-yr-old girl developed a chest infection which was treated successfully with penicillin. Five days later, while eating an apple, she choked suddenly, developed marked stridor and became cyanosed. Her father applied Heimlich's manoeuvre and back blows which cleared the airway, but within a few minutes she obstructed again and was brought

to the hospital. The intermittent nature of the obstruction was very deceptive. On arrival of the child at the hospital, the casualty Senior House Officer noted that she had marked inspiratory and expiratory stridor, was very restless, deeply cyanosed and had a tachycardia of 140 beat min⁻¹. However, a Consultant Anaesthetist examined the patient 15 min later and found the patient relaxed, calm and pink with no signs of obstruction. In view of this intermittent improvement, she was taken to the x-ray department for the radiographic examination of the neck and chest. The neck radiograph showed a post-cricoid swelling caused by the foreign body. A postero-anterior chest radiograph was taken, but before the film could be developed the patients's airway obstructed again. It was decided therefore, to proceed with bronchoscopy under general anaesthesia and the child was transferred to an operating theatre. Anaesthesia was induced with increasing concentrations of halothane in 100% oxygen. Bronchoscopy showed no foreign body and a normal trachea to a distance of 15 cm from the teeth, but marked narrowing beyond that. It was possible to pass the bronchoscope into the right main bronchus with difficulty, but the lumen of the left main bronchus was obliterated almost completely by external compression.

The chest radiograph showed a widened mediastinum (fig. 1) and a large mediastinal tumour mimicking upper airway obstruction was thought likely. Further surgical intervention was not

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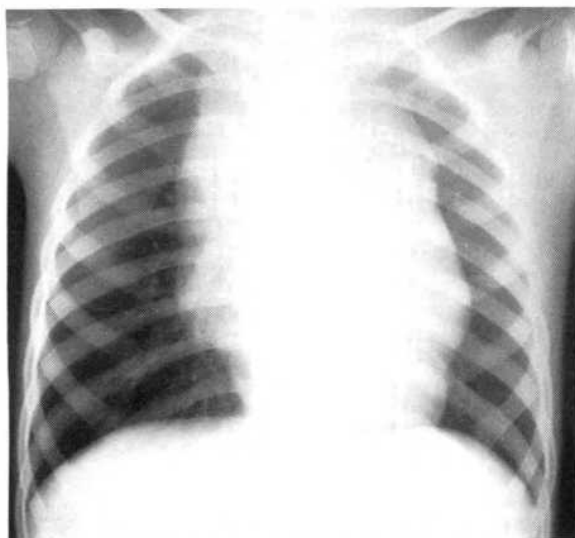


FIG. 1. Chest x-ray showing widening of the mediastinum.



FIG. 2. CT scan of the chest at the level of the third thoracic vertebra, showing tracheal compression by the anterior mediastinal mass.

necessary and anaesthesia was discontinued, precipitating a bout of coughing and total respiratory obstruction. The trachea was re-intubated and manual ventilation attempted, but it proved impossible to inflate the lungs and the patient became very cyanosed. The application of an increased positive airway pressure and a change to the lateral position allowed re-establishment of ventilation, and the patient was transferred to the Paediatric Intensive Care Unit.

Controlled mechanical ventilation with a positive end-expiratory pressure (PEEP) of 15 cm H₂O was required to maintain airway patency and to prevent distal air trapping. Computed tom-



FIG. 3. CT scan of the chest at the level of the fifth thoracic vertebra, showing marked bronchial compression.

ography (CT) of the chest was carried out and showed a large anterior mediastinal mass compressing the trachea (fig. 2) and main bronchi (fig. 3). A diagnosis of acute T-cell lymphoblastic leukaemia was made on bone marrow examination. The tumour responded to steroid and cytotoxic chemotherapy and the mass decreased rapidly in size and was almost invisible on the chest radiograph by the 5th day of treatment. The patient was weaned easily from the ventilator and the trachea was extubated on the 6th day. She was transferred to the haematology ward on the 7th day and was discharged home after successfully completing the first course of chemotherapy.

DISCUSSION

Approximately 60% of children with mediastinal masses present with respiratory symptoms [1]. These tumours may be neoplastic (Hodgkin's lymphomas, teratoma, lymphoblastic leukaemia) or benign (cystic hygroma, bronchogenic cyst). A large tumour mass may cause external compression of the trachea and bronchi or infiltrate the lumen. Intermittent airway obstruction may be caused by the movement of the heart during the cardiac cycle [2], but is usually caused by compression of the trachea. Symptoms are worse with lying supine, as the compression increases; patients prefer sitting up. Structures adjacent to the trachea (superior vena cava, pulmonary arteries and myocardium) may also be involved [3] and in severe cases local compression may drastically reduce right ventricular output, which may lead to cardiac arrest and death [4]. If biopsy for a tissue diagnosis is required, it should be

performed under local anaesthesia. General anaesthesia in these patients may be fatal [5], and ideally should be performed only when efforts to shrink the size of the tumour with appropriate treatment have been successful [6].

A history of progressive dyspnoea, chest infection and inability to lie flat should alert the anaesthetist to the possibility of complete airway obstruction on induction of anaesthesia. A chest CT scan quantifies the degree of airway compression, which is not always obvious on plain x-ray of the chest or conventional tomography [7, 8]. A 35% decrease in the diameter of the tracheal lumen is associated with ventilatory symptoms, while a greater than 50% decrease may be associated with complete obstruction during anaesthesia [1]. Cardiac investigations should include electrocardiogram and echocardiography [9].

Anaesthesia may have to be induced with the patient in the sitting position, which poses problems of access. A gaseous induction with halothane in oxygen and avoidance of neuromuscular blocking agents help to preserve a patent airway. If obstruction develops during anaesthesia, turning the patient to the semi-prone position may relieve obstruction by reducing the weight of tumour on the trachea [10]. Direct laryngoscopy also has been reported to relieve complete obstruction, presumably by putting the trachea under tension, thereby straightening it [11]. A rigid bronchoscope may pass the obstruction and may prove life saving. In the most extreme cases, femoro-femoral cardiopulmonary bypass may have to be considered [12].

The above case report illustrates a difficult clinical situation in which a mediastinal tumour in a child mimicked inhalation of a foreign body. The history, clinical examination and lateral neck x-ray proved misleading. The clinically deteriorating condition of the patient necessitated general anaesthesia, which should be avoided in

patients with mediastinal tumours. Under general anaesthesia, the patient developed complete obstruction which was relieved with great difficulty using continuous positive airway pressure and changes in posture.

REFERENCES

1. Azizkhan RG, Dudgeon DL, Buck JR, Colombani PM, Yaster M, Nichols D, Civin C, Kramer SS, Haller JA. Life threatening airway obstruction as a complication to the management of mediastinal masses in children. *Journal of Paediatric Surgery* 1985; 20: 816-822.
2. Fletcher R, Nordstrom L. The effects on gas exchange of a large mediastinal tumour. *Anaesthesia* 1986; 41: 135-138.
3. Lokich JJ, Goodman R. Superior vena cava syndrome, clinical management. *Journal of the American Medical Association* 1978; 231: 58-61.
4. Levin H, Bursztein S, Heifetz M. Cardiac arrest in a child with an anterior mediastinal mass. *Anesthesia and Analgesia* 1985; 64: 1129-1130.
5. Halpern S, Chatten J, Meadows AT, Byrd R, Lange B. Anterior mediastinal masses: Anesthesia hazard and other problems. *Journal of Pediatrics* 1983; 102: 407-410.
6. Piro AH, Weiss DR, Hellman S. Mediastinal Hodgkin's disease: a possible danger for intubation anaesthesia. *International Journal of Radiation Oncology, Biology, Physics* 1976; 1: 415-419.
7. Kirks DR, Fram EK, Effmann EL. Chest computed tomography for the evaluation of extrinsic airway compression. *American Journal of Roentgenology* 1982; 139: 1035.
8. Kirks DR, Korobkin M. Computed tomography of the chest in infants and children: techniques and mediastinal evaluation. *Radiologic Clinics of North America* 1981; 19: 409-419.
9. Neuman GG, Weingarten AE, Abramowitz RM, Kushins LG, Abramson AL, Ladner W. The anesthetic management of the patient with an anterior mediastinal mass. *Anesthesiology* 1984; 60: 144-147.
10. Bray RJ, Fernandes FJ. Mediastinal tumour causing airway obstruction in anaesthetized children. *Anaesthesia* 1982; 37: 571-575.
11. DeSoto H. Direct laryngoscopy as an aid to relieve airway obstruction in a patient with mediastinal mass. *Anesthesiology* 1987; 67: 116-117.
12. Hall KD, Friedman M. Extracorporeal oxygenation for the induction of anesthesia in a patient with an intrathoracic tumour. *Anesthesiology* 1975; 42: 493-495.

TRANSIENT ISCHAEMIC ATTACK AFTER SPINAL ANAESTHESIA

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SUMMARY

A case of transient ischaemic attack lasting 6 h occurred after spinal anaesthesia with bupivacaine. The level of sensory block was satisfactory and there was no significant hypotension. We discuss the possible cause of this previously undescribed complication.

KEY WORDS

Anaesthetic techniques, regional: spinal. Complications: cerebral ischaemia, transient.

Spinal anaesthesia is associated frequently with side effects such as hypotension, low back pain and headache. Neurological complications described include subdural haematoma [1], cerebral uncal herniation [2], intracranial haemorrhage [3], paresis of cranial nerves [4-6], pneumocephalus [7], visual disturbance [8, 9] and sensory and motor deficit at and below the level of dural puncture [10]. Convulsions and temporary hemiparesis have been described after spinal anaesthesia in a child with Moyamoya disease [11]. Unexplained hemiplegia and retrobulbar neuritis has also been reported in a healthy patient after hydrocele repair under spinal anaesthesia [12]. We describe a case of transient ischaemic attack characterized by loss of consciousness and temporary hemiparesis after induction of spinal anaesthesia in a healthy 58-yr-old male. There was no associated hypotension.

CASE REPORT

A 58-yr-old male presented with benign prostatic hypertrophy for transurethral prostatic resection. Pre-anaesthetic assessment revealed a history of hypertension, controlled well with atenolol. He was a non-smoker and had no other relevant past

medical history. On examination he weighed 85 kg, cardiovascular system was normal with arterial pressure of 120/80 mm Hg and there were no carotid bruits. ECG, haemoglobin and serum concentrations of urea and electrolytes were normal. Premedication comprised papaveretum 20 mg and hyoscine 0.4 mg i.m. 1 h before operation.

On arrival of the patient in the anaesthetic room, a vein was cannulated and ECG and non-invasive arterial pressure monitoring attached. Systolic arterial pressure was 160 mm Hg. An i.v. preload of Hartmann's solution 750 ml was commenced and midazolam 4 mg given i.v., resulting in satisfactory sedation. Initial attempts at spinal anaesthesia were unsuccessful at L4-5 because of inability to find the interspace. Dural puncture at L3-4 with a 26-gauge spinal needle was successful at the first attempt and plain 0.5% bupivacaine 2.75 ml was injected. Arterial pressure was measured at 3-min intervals and the level of sensory block was T10 bilaterally 25 min later. Systolic arterial pressure did not decrease to less than 110 mm Hg at any time and the patient remained alert and co-operative. He was transferred to the operating theatre and connected to ECG, non-invasive arterial pressure and pulse oximetry monitoring (Datex cardiocap).

As the procedure was about to commence, the patient became dysarthric then lost consciousness and became apnoeic. His lungs were ventilated with 100% oxygen by face mask; arterial pressure was 120 mm Hg systolic. Ephedrine 10 mg was given i.v. as it was thought that this reading might be incorrect, and subsequent arterial pressure was found to be 140/90 mm Hg. Initially, a diagnosis

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of high spinal block was considered, but the patient responded to pain originating above the level of T10. The period of apnoea lasted only about 5 min and resolved spontaneously. The patient's conscious state improved also, such that he was able to maintain his own airway. Arterial pressure and pulse oximetry saturation measurements remained normal. The lack of a temporal relationship between the administration of any drug and the sudden onset of symptoms made a pharmacological effect unlikely, but flumazenil (100- μ g boluses to a total of 400 μ g) and naloxone (50- μ g boluses to a total of 700 μ g) were given i.v. to antagonize any benzodiazepine or opioid effect, without improvement. The patient remained semiconscious, with signs of a left hemiparesis.

Surgery was cancelled and the patient transferred to the intensive care unit. Arterial blood-gas tensions, serum concentrations of urea and electrolytes, cardiac enzymes, blood glucose concentrations and 12-lead ECG were normal. An urgent computed tomographic (CT) brain scan was performed and showed no focal abnormality or evidence of intracranial bleed. Contrast medium enhancement was not used as it was felt that this would add little additional information and the patient's symptoms were resolving. Over the following 6 h the patient made a full recovery and had no recollection of the event. A diagnosis of transient ischaemic attack was made and the patient was referred to the physicians for further investigation. Serial cardiac enzymes, ECG and echocardiogram were normal. Carotid angiography was not performed in view of his full recovery.

The patient has been followed up for 9 months. He has been seen by a neurologist, whose opinion was that this was a brainstem event consequent upon the adverse haemodynamic effects of the spinal anaesthetic. He has remained totally asymptomatic with respect to any further cerebral events. On further questioning, however, a strong family history of cerebrovascular disease was elicited. His prostatic symptoms have improved and he has declined further surgery and investigations.

DISCUSSION

Sudden loss of consciousness after spinal anaesthesia with local anaesthetics may be caused by cardiovascular decompensation or a total spinal anaesthetic. When associated with hemiparesis,

this implies more localized cerebral ischaemia. A transient ischaemic attack, cerebral infarction either embolic or haemorrhagic, or spontaneous subarachnoid haemorrhage are also possible diagnoses. The presence of a pre-existing disorder such as intracranial tumour, encephalitis or multiple sclerosis should be considered. Spinal anaesthesia may also precipitate pre-existing neurological disease [13]. In our patient, a diagnosis of transient ischaemic attack was confirmed by the spontaneous recovery within 24 h and normal CT scan. No significant change in heart rate or arterial pressure occurred, but we accept that, with intermittent non-invasive pressure monitoring there may have been periods of pressures less than those recorded. The onset and duration of symptoms correlated well with that of the spinal anaesthesia and it is unlikely that this attack was a purely coincidental event. We feel, however, that there are similarities between our patient and the case described of a child with Moyamoya disease [11]. In that patient, convulsions and hemiparesis lasting 10 days occurred after spinal anaesthesia. In both patients, symptoms of cerebral ischaemia occurred despite cardiovascular stability and there was good recovery.

Moyamoya disease is a syndrome with which there is a compromised cerebral circulation caused by bilateral stenosis and obstruction of major cerebral vessels and development of a vascular network at the base of the brain [14, 15]. This results in symptoms of cerebral ischaemia, usually in the form of transient ischaemic attacks. Without cerebral angiography, we have no conclusive evidence, but propose that our patient also had a compromised cerebral circulation caused by accelerated atheroma secondary to hypertension. He had a strong family history of cerebrovascular disease and, although he had no previous history of transient ischaemic attacks, blood flow to an area with critical cerebral perfusion could have decreased to less than adequate levels. This could occur without a large change in arterial pressure, because changes in cardiac output may have been more important. Even if arterial pressure is maintained by compensatory vasoconstriction above the level of a spinal block, cerebral blood flow may be reduced [16, 17].

In conclusion, we have observed a previously unreported complication following spinal anaesthesia. We suggest that this was a brainstem transient ischaemic attack consequent upon the

adverse haemodynamic effects of spinal anaesthesia in a susceptible individual.

REFERENCES

1. Jonsson LO, Einarsson P, Olsson GL. Subdural haematoma and spinal anaesthesia. *Anaesthesia* 1983; **38**: 144-146.
2. Eerola M, Kaukinen L, Kaukinen S. Fatal brain lesion following spinal anaesthesia. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 115-116.
3. Mantia AM. Clinical report of the occurrence of an intracranial hemorrhage following post-lumbar headache. *Anesthesiology* 1981; **55**: 684-685.
4. Wang LP, Fog J, Bove M. Transient hearing loss following spinal anaesthesia. *Anaesthesia* 1987; **42**: 1258-1263.
5. Richer S, Ritacca D. Sixth nerve palsy after lumbar anaesthesia. *Optometry and Vision Science* 1989; **66**: 320-321.
6. King RA, Calhoun JH. Fourth cranial nerve palsy following spinal anaesthesia. *Journal of Clinical Neuro-ophthalmology* 1987; **7**: 20-22.
7. Roderick L, Moore DC, Artru AA. Pneumocephalus with headache during spinal anesthesia. *Anesthesiology* 1985; **62**: 690-692.
8. Stoll MR. Pericentral ring scotoma. *Archives of Ophthalmology* 1950; **43**: 66-91.
9. De Lange JJ, Stilma JS, Crezee F. Visual disturbances after spinal anaesthesia. *Anaesthesia* 1988; **43**: 570-572.
10. Kane RE. Neurologic deficits following epidural or spinal anesthesia. *Anesthesia and Analgesia* 1981; **60**: 150-161.
11. Yasukawa M, Yasukawa K, Akawaga S, Nakagawa Y, Miyasaka K. Convulsions and temporary hemiparesis following spinal anesthesia in a child with Moyamoya disease. *Anesthesiology* 1988; **69**: 1023-1024.
12. Ghate SV, Kulkarni SG, Sarate GS. Hemiplegia and retrobulbar neuritis after subarachnoid block. *Canadian Anaesthetists Society Journal* 1981; **28**: 283-284.
13. Fleiss AN. Multiple sclerosis appearing after spinal anesthesia. *New York State Journal of Medicine* 1949; **49**: 1076-1077.
14. Brown SC, Lam AM. Moyamoya disease—A review of experience and anaesthetic management. *Canadian Journal of Anaesthesia* 1987; **34**: 71-75.
15. Warlow CP. Cerebrovascular disease. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*. Oxford: Oxford University Press. Vol. 2. 1984; 21-71.
16. Sancetta SM, Lynn RB, Simeone FA, Scott RW. Studies in hemodynamic changes in humans following induction of high and low spinal anesthesia. *Circulation* 1952; **6**: 559-575.
17. Lee AJ, Atkinson RS, Watt MJ, eds. Physiology of central neural blockade. In: *Sir Robert Macintosh's Lumbar Puncture And Spinal Analgesia*, 5th Edn. Edinburgh: Churchill Livingstone, 1985; 98-117.

TEMPERATURE DEPENDENCE OF LED AND ITS THEORETICAL EFFECT ON PULSE OXIMETRY

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SUMMARY

Ambient temperature is known to affect the emission spectrum of a light-emitting diode (LED). This study has investigated the effect of changes in ambient temperature on the emission spectra of two LED with peak emission wavelengths similar to those used in pulse oximetry. There was a 5.5-nm increase in the peak wavelength for a 660-nm LED, and a 7.8-nm increase in the peak wavelength for a 950-nm LED as temperature increased from 0 to 50 °C. Using a simple theoretical model based on the Beer-Lambert law, the effect of these shifts in wavelength on pulse oximeter accuracy was examined and found to be negligible over the temperature range studied.

KEY WORDS

Equipment: pulse oximeters. Monitoring: pulse oximeters.

The mode of operation of the pulse oximeter has been described previously [1]. Pulse oximeter probes normally contain two light-emitting diodes (LED) which typically emit red (660-nm) and infra-red (950-nm) light. However, it has been suggested [2] that problems may occur with the pulse oximeter as a result of temperature dependent changes in performance of the LED.

It is known that the peak wavelength of the emitted radiation from an LED changes with ambient temperature. LED are semiconductor devices and light is emitted when an electron acquires sufficient energy to cross the forbidden energy gap, E_g . When this electron returns to a lower energy level, a photon is emitted with a wavelength, λ , which is related to the energy gap of the semiconductor by $E_g = hc/\lambda$, where h is the Planck constant ($= 6.626 \times 10^{-34}$ Js) and c is the speed of light in a vacuum ($= 2.998 \times 10^8$ ms⁻¹). The magnitude of E_g depends on temperature

[3, 4]; in most common semiconductor materials, E_g decreases as temperature increases. Thus the peak emission wavelength of an LED should increase with temperature, as λ is inversely proportional to E_g .

Oxygen saturation is monitored usually in heated clinical environments, but pulse oximeters are used occasionally in extreme temperatures, for example, by the roadside [5]. Most manufacturers quote an operating temperature range of 0-50 °C (table I). The shift in wavelength of the LED with temperature has been anticipated by one manufacturer (Physio-Control, Lifestat 1600) and a temperature sensor diode has been included in their oximeter probe.

The purpose of this study was to determine the shifts in emission spectra of both red and infra-red LED, produced by changing the ambient

TABLE I. Pulse oximeter operating temperature ranges given by manufacturers. *Temperature sensor diode included in Physio-Control oximeter probe

Manufacturer	Pulse oximeter	Operating range (°C)	
		Min.	Max.
Physio-Control	Lifestat 1600	0	45*
Sensormedics	Oxyshuttle	15	40
Minolta	Pulsox 7	None specified	
Nonin	8604	10	45
Kontron	7840	15	40
Novamatrix	515	10	40
Datex	Satlite	10	35
Nellcor	N-200	0	40
Ohmeda	Biox 3700	0	50

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TABLE II. *Electro-optical LED characteristics*

LED type	Wavelength (nm)	Output power
TLMP 7005	660	500 mcd at 50 mA
TSUS 5402	950	15 mW at 100 mA

temperature from 0 to 50 °C. A theoretical model was then used to predict the effect of these shifts on the accuracy of pulse oximeter saturation readings.

MATERIALS AND METHODS

The spectra of the LED were measured using a Czerny–Turner type monochromator. Two LED were investigated (table II): one with peak emission wavelength, λ_{peak} , at a nominal 660 nm (*R*), and one with λ_{peak} at 950 nm (*IR*), these wavelengths being typical of those used in pulse oximetry. Each LED in turn was mounted in a holder in front of the spectrometer, and was modulated with a square wave signal at 1 kHz. The modulating signal had a 50 % duty cycle, and the maximum current specified on the data sheet (table II) was passed through the LED during the “on” part of the cycle. The LED in commercial pulse oximeters are pulsed typically at between 0.5 and 1.5 kHz, with a duty cycle of 2–50 % depending on the make of oximeter. A 50 % duty cycle was chosen for our experiments, as the heating effect is greatest under these conditions.

The light from the LED was focused through the input slit of the spectrometer and, by varying the angle of incidence onto a reflection grating, a range of wavelengths from 600 nm to 1000 nm was obtained. The spectrometer uses a germanium photodiode to measure the output light intensity at each wavelength. A transimpedance

and lock-in amplifier completed the arrangement (fig. 1).

The holder in which the LED were mounted contained a hollow channel through which water from a temperature controlled reservoir was pumped (fig. 2). The walls of the holder were very thin in order to optimize thermal contact between the water and the LED. By adjusting the temperature of the water in the reservoir, the ambient temperature of the LED was changed. The water temperature in the reservoir was measured using a mercury-in-glass thermometer

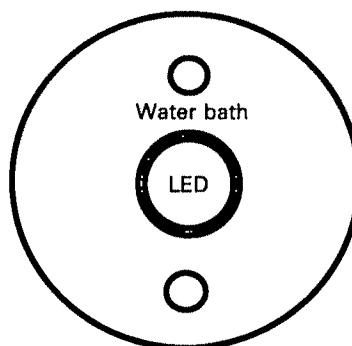
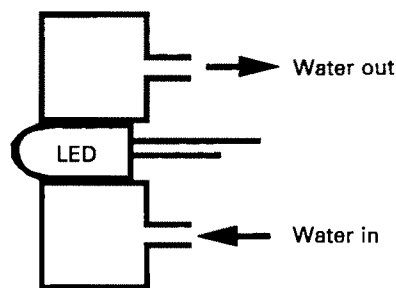


FIG. 2. Cross-sections of the water-filled holder used to mount the LED in front of the spectrometer.

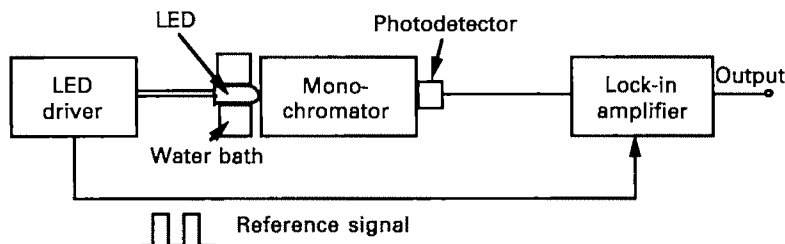


FIG. 1. Diagram of apparatus used to measure the emission spectrum of an LED at ambient temperatures between 0 °C and 50 °C.

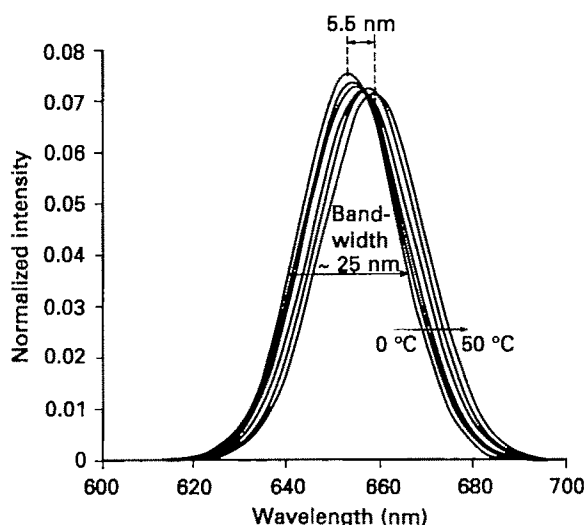


FIG. 3. Shift in emission spectrum of red LED as ambient temperature is increased from 0 °C to 50 °C in 10-°C steps.

immersed up to 10 cm. To minimize heat loss through the circuit, distances between the LED holder and the reservoir were small, and the temperature difference between water at the inlet and outlet of the reservoir was checked and found to be less than 1 °C.

The spectrum of each LED was measured at 2-nm intervals at ambient temperatures of 0, 10, 20, 30, 40 and 50 °C. The system was allowed to equilibrate for 10 min between the measurement of each spectrum.

Theoretical model to examine the effect of spectral shifts on pulse oximeter reading

As pulse oximeters are calibrated when the two LED are operating at their nominal wavelengths, it is possible that shifts in wavelength lead to inaccuracies in the oxygen saturation reading from the pulse oximeter (Sp_{O_2}). In order to estimate the error caused by a change in ambient temperature from 0 to 50 °C, we derived, as a first approximation, a simple mathematical relationship based on the Beer-Lambert law. This law relates the optical density (OD) of an absorbing (but non-scattering) solution to the concentration of absorber by

$$OD = \log_{10} (I_0/I) = \epsilon cd$$

where I_0 and I are the incident and transmitted light intensities respectively, through a sample of depth d , concentration c , and having an extinction coefficient ϵ .

For a solution containing n absorbers:

$$\text{total absorption} = \sum_{i=1}^n \epsilon_i c_i d_i$$

The ratio of the absorption at two wavelengths, 1 and 2, is:

$$R/IR = \beta = \frac{\sum_{i=1}^n \epsilon_{i1} c_i d_i}{\sum_{i=1}^n \epsilon_{i2} c_i d_i}$$

With two species of haemoglobin, oxygenated (subscript o) and reduced (subscript r), occupying the same depth, this becomes:

$$\beta = \frac{\epsilon_{1o}c_{1o} + \epsilon_{1r}c_{1r}}{\epsilon_{2o}c_{2o} + \epsilon_{2r}c_{2r}} \quad (1)$$

If we define the saturation of a species i as $S_i = (c_i/c)$, where c is the total haemoglobin concentration, then we have:

$$\beta = \frac{S_r \epsilon_{1r} + S_o \epsilon_{1o}}{S_r \epsilon_{2r} + S_o \epsilon_{2o}}$$

Now $S_r = 1 - S_o$. Substituting into (1) and rearranging gives:

$$S_o = Sp_{O_2} = \frac{\epsilon_{1r} - \beta \epsilon_{2r}}{\epsilon_{1r} - \epsilon_{1o} + \beta(\epsilon_{2o} - \epsilon_{2r})} \quad (2)$$

which is the theoretical relationship for the oxygen saturation of blood when scattering is neglected. It should be remembered that Sp_{O_2} is expressed normally as a percentage, and equation (2) should therefore be multiplied by 100 %.

Calculation of the effective extinction coefficients

While LED have narrow-band spectral outputs, they cannot be considered to be monochromatic. It is preferable, therefore, to compute "effective extinction coefficients" for oxyhaemoglobin (HbO_2) and haemoglobin (Hb), taking into account the spectral distribution, rather than using the values of extinction coefficients at the peak emission wavelengths. The effective extinction coefficients are computed by summing the products of the normalized LED intensity value and the extinction coefficient every 2 nm over the whole spectrum. That is:

$$\epsilon^{eff} = \sum_{\lambda} I(\lambda) \epsilon(\lambda)$$

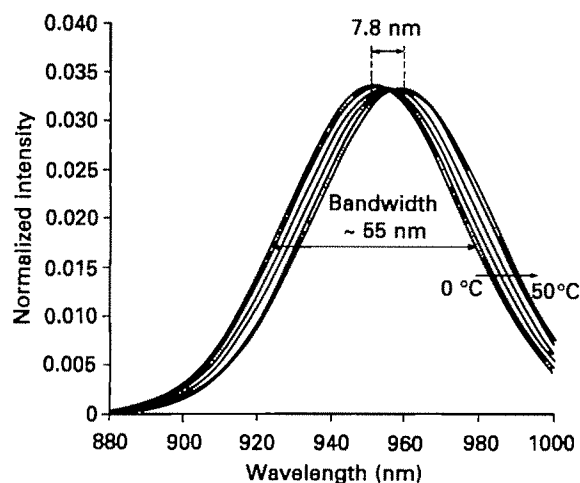


FIG. 4. Shift in emission spectrum of infra-red LED as ambient temperature is increased from 0 °C to 50 °C in 10-°C steps.

The extinction coefficients, $\epsilon(\lambda)$, of HbO_2 and Hb were obtained previously at 2-nm intervals using a Shimadzu UV-160 double beam scanning spectrophotometer [6].

RESULTS

The measured spectra for the red and infra-red LED, respectively, are shown in figures 3 and 4. Each spectrum has been normalized by setting the sum of the intensity values, $I(\lambda)$, measured at 2-nm intervals, equal to 1. The results in figure 3 show a steady increase in peak emission wavelength of the red LED as temperature is increased from 0 to 50 °C, with an overall shift of 5.5 nm. Figure 4 shows a shift of the infra-red spectrum of 7.8 nm in the same direction for the same increase in temperature.

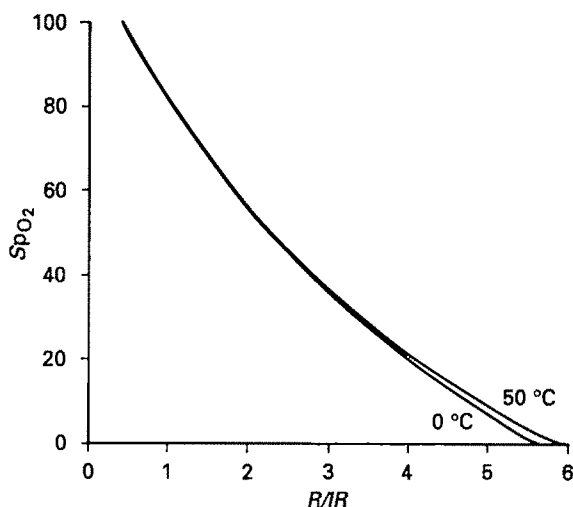


FIG. 5. Pulse oximeter saturation reading (SpO_2) plotted against red/infra-red ratio (R/IR) according to equation (2), at ambient temperatures of 0 °C and 50 °C. Equation (2) was derived using the Beer-Lambert law.

From figures 3 and 4, the half-intensity spectral bandwidths may be measured to be 25 nm for the red LED and 55 nm for the infra-red LED, although the spectral bandwidth did not change significantly with either LED. The effective extinction coefficients of HbO_2 and Hb at each temperature were evaluated using the method described. These values (table III) were substituted into equation (2), and the values of SpO_2 calculated from this equation were plotted against the R/IR ratio at 0 and 50 °C (fig. 5).

DISCUSSION

A shift of 5.5 nm in red LED peak wavelength, and of 7.8 nm in infra-red LED peak wavelength caused negligible change in the value of SpO_2 .

TABLE III. Effective extinction coefficients of oxyhaemoglobin (HbO_2) and reduced haemoglobin (Hb)

Temperature (°C)	Red		Infra-red	
	HbO_2 ϵ_{10} (litre $\text{mmol}^{-1} \text{cm}^{-1}$)	Hb ϵ_{1r} (litre $\text{mmol}^{-1} \text{cm}^{-1}$)	HbO_2 ϵ_{20} (litre $\text{mmol}^{-1} \text{cm}^{-1}$)	Hb ϵ_{2r} (litre $\text{mmol}^{-1} \text{cm}^{-1}$)
0	0.123	0.856	0.274	0.153
10	0.122	0.849	0.273	0.151
20	0.121	0.845	0.271	0.148
30	0.119	0.832	0.269	0.145
40	0.118	0.823	0.267	0.141
50	0.117	0.811	0.265	0.139

calculated from equation (2) (fig. 5). Thus, to a first approximation, a change in the ambient temperature of the LED from 0 to 50 °C should not affect the accuracy of pulse oximeter readings.

The temperature dependence of the energy gap of semiconductors is well documented [3, 4]. The standard deviation of the energy gap at room temperature is approximately 0.1% [7], and for a given change in temperature, the uncertainty in the magnitude of the wavelength shift is of the same order of magnitude. This spread of values for wavelength shift is small enough not to affect our conclusion. In contrast, there is a variation of up to ± 15 nm in the peak wavelength of different LED of the same type, because of production tolerances. This problem is overcome in commercial pulse oximeters by the inclusion of a coding resistor in the probe connector which allows the oximeter to select a calibration curve appropriate to the wavelengths of the LED in that particular probe [8].

It should be remembered that the relationship between Sp_{O_2} and R/IR , β , given in equation (2), was derived using the Beer-Lambert law. However, it is well-known that whole blood does not behave as a simple absorbing substance, and that light is scattered repeatedly by the red blood cells [9]. Thus equation (2) is only an approximation and pulse oximeters are usually calibrated empirically using data obtained by inducing hypoxia in healthy volunteers. Nonetheless, the model based on equation (2) does give a good indication of the effect of changes in extinction coefficients on the estimation of Sp_{O_2} . It is unlikely, therefore, that the shift of LED emission spectra with ambient temperature affects the pulse oximeter reading in most clinical situations.

Other factors, however, may cause inaccuracies in Sp_{O_2} readings at extreme temperatures. In states of extreme cold, for example, there is a generalized cutaneous vasoconstriction and reduced blood flow, while in hot temperatures vasodilatation occurs and blood flow is increased. These effects are particularly marked in the extremities of the body, for example in the finger.

Vasoconstriction of the peripheral vascular bed induced by cold exposure may reduce significantly the amplitude of the a.c. signals received by the pulse oximeter [10]. While there is little conclusive evidence on the effects of perfusion on pulse oximetry, the failure of any signal to be detected in states of low perfusion has been noted on several occasions [11-15].

The reduced amplitude of the a.c. signals occurring during cold exposure causes the pulse oximeter to be more sensitive to motion artefacts, for example those caused by shivering or coughing. These artefacts may cause the pulse oximeter to give an erroneous value of Sp_{O_2} [16].

Further consequences of exposure of the body to cold temperatures include a reduced oxygen uptake by the cold skin, and a cold induced shift to the left of the HbO_2 dissociation curve. This causes the oxygen saturation of the blood to increase, especially in the extremities of the body which are at a lesser temperature than the core temperature. Thus the oxygen saturation measured across the finger by a pulse oximeter may not give a correct indication of the oxygen saturation of the blood in the main body circulation, even though it may be giving a correct value for the saturation of the blood in the finger.

We conclude that inaccuracies in pulse oximeter readings in extreme temperatures are far more likely to be caused by changes in peripheral perfusion, rather than a result of the temperature dependence of the light sources in the pulse oximeter probe.

REFERENCES

1. Wukitch MW, Petterson MT, Tobler DR, Pologe JA. Pulse oximetry: analysis of theory, technology, and practice. *Journal of Clinical Monitoring* 1988; 4: 290-301.
2. Falconer RJ, Robinson BJ. Comparison of pulse oximeters: accuracy at low arterial pressure in volunteers. *British Journal of Anaesthesia* 1990; 65: 552-557.
3. Varshni YP. Temperature dependence of the energy gap in semiconductors. *Physica* 1967; 34: 149-154.
4. Panish MB, Casey HC jr. Temperature dependence of the energy gap in GaAs and GaP. *Journal of Applied Physics* 1969; 40: 163-167.
5. Silverston P. Pulse oximetry at the roadside; a study of pulse oximetry in immediate care. *British Medical Journal* 1989; 298: 711-713.
6. de Kock JP, Reynolds KJ, Tarassenko L, Moyle JTB. The effect of varying LED intensity on pulse oximeter accuracy. *Journal of Medical Engineering & Technology* 1991; 15: 111-115.
7. Thurmond CD. The standard thermodynamic functions for the formation of electrons and holes in Ge, Si, GaAs, and GaP. *Journal of the Electrochemical Society* 1975; 122: 1133-1141.
8. Pologe JA. Pulse oximetry: technical aspects of machine design. *International Anesthesiology Clinics* 1987; 25: 137-153.
9. Anderson NM, Sekelj P. Light-absorbing and scattering properties of non-haemolysed blood. *Physics in Medicine and Biology* 1967; 12: 173-184.

10. Kurki TS, Piirainen HI, Kurki PT. Non-invasive monitoring of finger arterial pressure in patients with Raynaud's phenomenon: effects of exposure to cold. *British Journal of Anaesthesia* 1990; **65**: 558-563.
11. Mihm FG, Halperin BD. Noninvasive detection of profound arterial desaturations using a pulse oximetry device. *Anesthesiology* 1985; **62**: 85-87.
12. Tremper KK, Hufstedler SM, Barker SJ, Adams AL, Wong DH, Zaccari J, Benik K, Lemons V. Accuracy of a pulse oximeter in the critically ill adult: effect of temperature and hemodynamics. *Anesthesiology* 1985; **63**: A175.
13. Lawson D, Norley I, Korbon G, Loeb R, Ellis J. Blood flow limits and pulse oximeter detection. *Anesthesiology* 1987; **67**: 599-603.
14. Wilkins CJ, Moores M, Hanning CD. Comparison of pulse oximeters: effects of vasoconstriction and venous engorgement. *British Journal of Anaesthesia* 1989; **62**: 439-444.
15. Langton JA, Lassey D, Hanning CD. Comparison of four pulse oximeters: effects of venous occlusion and cold-induced peripheral vasoconstriction. *British Journal of Anaesthesia* 1990; **65**: 245-247.
16. Langton JA, Hanning CD. Effect of motion artefact on pulse oximeters: evaluation of four instruments and finger probes. *British Journal of Anaesthesia* 1990; **65**: 564-570.

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

MANCHESTER MEETING

July 12-13, 1991

(The name of the author presenting the paper is shown in bold type. * Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

EFFECT OF SUPINE AND LATERAL POSITIONS ON AIRWAY PATENCY IN ANAESTHETIZED PATIENTS

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Recent studies have renewed interest in the mechanisms of airway obstruction in anaesthetized patients. We have studied the effect of the two most common patient positions (supine and lateral) on the degree of head extension necessary to maintain a clear airway in anaesthetized, spontaneously breathing patients.

Thirty-five patients gave informed consent to the study. All had disease-free airways and normal head and neck movements. At the end of minor surgery, anaesthesia was continued via a well-fitting face mask and circle system. Patients were lying supine on a hard flat surface without additional head support. Expired tidal volumes were measured using a volumeter. Head extension was varied until a clear airway could be maintained; this was indicated by a maximal expired tidal volume. The angle of head extension was recorded as the angle between the horizontal surface and a line joining the tragus of the ear and the lateral corner of the eye. The patients were then turned to the lateral position with a hard flat surface apposed to the back of the occiput and scapulae. The same manoeuvre and measurements were repeated.

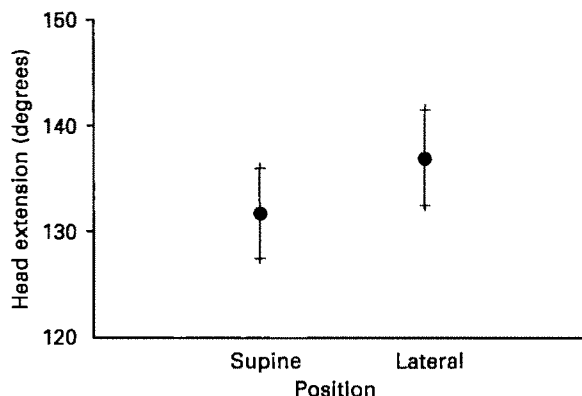


FIG. 1. Head extension (median, interquartile range) to maintain airway in the supine and lateral positions.

Three patients developed airway obstruction despite maximal head extension and were excluded from analysis. The remaining 32 patients required less head extension in the supine position (median 132 degrees, interquartile range 127.5-136 degrees) than in the lateral position (median 137 degrees, interquartile range 132.5-141.5 degrees) ($P < 0.001$, Wilcoxon test) (fig. 1).

The traditional concept of the mechanism of upper airway obstruction in anaesthetized patients was that the tongue fell back against the posterior pharyngeal wall. This view was supported by radiographic studies by Safar, Escarraga and Chang [1] who advocated that backward tilt of the head would separate the base of the tongue from the pharyngeal wall. It would be reasonable to expect greater head extension in the supine than in the lateral position since the tongue would fall back more easily under gravity. However, our study shows that it is easier to maintain the airway in the supine position. We have not demonstrated the mechanism involved.

REFERENCE

1. Safar P, Escarraga LA, Chang F. *Journal of Applied Physiology* 1959; 14: 760-764.

MORBIDITY FOLLOWING DAY-CASE PROCEDURES

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Our previous presentations to the Society have revealed a surprisingly high incidence of postoperative morbidity in day-case dental patients [1] which is not improved by abolition of suxamethonium pains [2]. We present here morbidity data after three common day-case procedures where suxamethonium pains have been prevented.

Twenty-four patients presenting for day-case gynaecological laparoscopic sterilization on a Saturday morning were given a standard anaesthetic technique of propofol, atracurium, fentanyl and ventilation with nitrous oxide in oxygen. Twelve patients were premedicated with diclofenac 50 mg orally 1 h before operation.

Twenty-six patients presenting on a midweek afternoon day-case list for dental extractions were allocated to two groups. Half of the patients were allowed to breathe spon-

TABLE I. Operation site pain (0-3) and activity (0-3) scores (total score/maximum score) in the three groups

	Operation site pain		Activity	
	Day 1	Day 2	Day 1	Day 2
Gynaecological (n = 24)	36/72	—	33/72	—
Dental (n = 26)	38/78	37/78	38/78	52/78
Orthopaedic (n = 12)	18/36	15/36	18/36	19/36

taneously after tracheal intubation using suxamethonium, but after administration of alcuronium 2 mg to prevent muscle pains. In the remaining patients, the trachea was intubated using atracurium and ventilation was with nitrous oxide in oxygen.

Twelve patients on a morning midweek list for day-case arthroscopy were anaesthetized using propofol, fentanyl and spontaneous ventilation with isoflurane and nitrous oxide in oxygen.

All patients were seen on the 1st and usually 2nd day after operation by one of the investigators unaware of the anaesthetic technique used. They were assessed for operation site pain (0-3) and activity (0 = in bed, 3 = full activity) as in our previous studies (table I).

Operation site pain was similar in all three groups. The greater overall activity in the gynaecological group is surprising since until recently this procedure was considered unsuitable for day-case management. Some of the observed differences in activity might, however, be a result of the different days of the week and time of day that the three procedures were undertaken.

Although pain scores in the orthopaedic group were similar to the other groups, there was no reduction on the 2nd day. Overall activity was rather poor also on both days, but may be more affected by the site of operation.

Our preliminary findings suggest that day-case morbidity may be reduced by improvement in surgical and anaesthetic (as well as administration of analgesia) skills.

REFERENCES

1. Smith SO, Laurence AS, DeSilva F. *British Journal of Anaesthesia* 1990; 65: 284P.
2. DeSilva F, Smith SO, Laurence AS. *British Journal of Anaesthesia* 1990; 65: 588P.

COMPARISON OF INFUSION RATES OF THIOPENTONE FOR INDUCTION OF ANAESTHESIA IN ELDERLY PATIENTS

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In a previous study [1] where propofol was administered to patients aged 60 yr or more, a slower rate of infusion for induction of anaesthesia resulted in increased cardiovascular stability and a lower total dose. The aim of this study was to evaluate this effect using thiopentone, and to determine if this effect was reflected in alterations in plasma concentration.

TABLE II. Duration of induction of anaesthesia, total dose of thiopentone required and AUC values in patients receiving thiopentone 300 ml h⁻¹ (group 1), 600 ml h⁻¹ (group 2) and 1200 ml h⁻¹ (group 3) (mean (SD))

	Induction time (s)	Thiopentone (mg kg ⁻¹)	AUC (10 min) (µg ml ⁻¹ min ⁻¹)
Group 1	90.8 (19.3)	2.80 (0.37)	53.13 (10.82)
Group 2	57.4 (10.5)	3.63 (0.39)	71.94 (14.95)
Group 3	40.8 (6.7)	4.99 (0.96)	86.78 (35.56)
P value	< 0.001	< 0.001	< 0.05

After Ethics Committee approval and written informed consent, 30 patients ASA I or II, aged 60 yr or more were allocated randomly to receive 2.5% thiopentone at 300 ml h⁻¹ (group 1), 600 ml h⁻¹ (group 2) or 1200 ml h⁻¹ (group 3), for induction of anaesthesia using an Ohmeda 9000 infusion pump. Temazepam 20 mg orally was given 1 h before surgery, and all patients received fentanyl 0.75 µg kg⁻¹ 5 min before induction. The end of induction of anaesthesia was defined as loss of verbal contact with the patient. The patient then breathed 66% nitrous oxide in oxygen, supplemented by enflurane according to clinical requirements. Monitoring throughout consisted of non-invasive arterial pressure (Dinamap), ECG and pulse oximetry. The duration of induction and total dose of thiopentone required were noted. Blood samples were obtained at 2, 5 and 10 min after induction for subsequent analysis of thiopentone by high performance liquid chromatography [2]. The area under the concentration-time curve was calculated for each patient using the trapezoidal rule. Data were analysed using ANOVA (SPSSX PC) and *P* < 0.05 was taken as significant.

There were no significant differences between the groups in sex, weight or ASA status. The patients in group 2 were significantly older than those in group 1 (*P* = 0.014). The method of induction of anaesthesia was smooth and no patient experienced discomfort. There were no significant differences between the groups in heart rate, mean arterial pressure or oxygen saturation. The induction time was significantly longer in patients receiving the slower infusions of thiopentone, but the total dose of induction agent was significantly smaller (table II). Concentrations of thiopentone were smaller in the groups receiving slower induction rates. This was significant for concentrations measured at 5 (*P* = 0.002) and 10 min (*P* = 0.003).

REFERENCES

1. Peacock JE, Lewis R, Hunter S, Reilly CS. *British Journal of Anaesthesia* 1990; 65: 346-352.
2. Toner W, Howard PJ, Dundee JW, McIlroy PDA. *Anaesthesia* 1979; 34: 656-660.

PROPOFOL INDUCES THE PRODUCTION OF ENDOTHELIUM-DERIVED RELAXING FACTOR

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Propofol reduces arterial pressure partly by decreasing sys-

TABLE III. cGMP production (geometric mean) in response to propofol from 3–7 separate cell batches. n = number of wells. * $P < 0.05$, ** $P < 0.01$ compared with control; †† $P < 0.01$ compared with propofol alone. (Data were log-transformed and a Dunnett's t test performed)

	n	cGMP (fmol/ cell $\times 10^6$)	95 % confidence interval
Krebs (control)	16	7.01	(5.7–8.7)
DMSO (0.1 % in Krebs)	12	6.70	(5.2–8.6)
10 % Lipid	12	7.02	(5.5–9.0)
SNP 100 $\mu\text{mol litre}^{-1}$	4	132.0**	(85.9–203.0)
Bradykinin 100 nmol litre $^{-1}$	3	29.96**	(18.2–49.2)
Propofol			
30 $\mu\text{mol litre}^{-1}$	8	10.38*	(7.7–14.1)
100 $\mu\text{mol litre}^{-1}$	14	14.47**	(11.5–18.2)
300 $\mu\text{mol litre}^{-1}$	13	30.44**	(24.0–38.7)
1 mmol litre $^{-1}$	12	36.29**	(28.3–46.5)
Propofol 100 $\mu\text{mol litre}^{-1}$	5	17.14	(11.7–25.2)
Propofol + nitro-arginine 100 $\mu\text{mol litre}^{-1}$	9	7.56††	(5.7–10.1)
Propofol + haemoglobin 10 $\mu\text{mol litre}^{-1}$	8	6.54††	(4.8–8.9)

temic vascular resistance (SVR). Endothelium-derived relaxing factor (EDRF), now identified as nitric oxide [1], is released from endothelial cells and increases guanosine 3',5'-cyclic monophosphate (cGMP) production in adjacent smooth muscle cells evoking relaxation. Given i.v., L-arginine, the physiological precursor of nitric oxide, reduces SVR [2]. Since nitric oxide is a potent vasodilator [1] we investigated if propofol could stimulate the release of nitric oxide from endothelium.

Porcine aortic endothelial cells were isolated using standard collagenase digestion techniques [3] and used between passage one to three. Porcine aortic smooth muscle cells were isolated from explants of porcine aorta and used between passage one and two. Co-cultures were prepared by seeding approximately equal numbers of endothelial cells and smooth muscle cells into a 24 well tray for use 24 h later. Before the experiments the co-cultures were rinsed twice in HEPES-buffered Krebs and incubated for 10 min with either propofol 30 $\mu\text{mol litre}^{-1}$ –1 mmol litre $^{-1}$ or propofol 100 $\mu\text{mol litre}^{-1}$ plus inhibitor. cGMP was extracted with HCl 0.1 mol litre $^{-1}$ and measured by specific radioimmunoassay.

Propofol stimulated the formation of cGMP in co-cultures in a dose-dependent manner (table III). Formation of cGMP was attributable to release of nitric oxide since the response was abolished in the presence of haemoglobin and antagonized by the specific inhibitor of nitric oxide synthase, N^G-nitro-L-arginine. Lipid 10 % had no effect. Cultures of smooth muscle cells alone did not respond to propofol as there was no increase in cGMP, although they responded to SNP ($n = 6$), thus confirming the endothelium-dependent nature of the propofol-induced nitric oxide response. It remains to be determined if the vasodilatation produced clinically by propofol is mediated by nitric oxide.

REFERENCES

- Palmer RMJ, Moncada S. *Nature* 1988; 333: 664–666.
- Petros AJ, Hewlett AM, Bogle RG, Pearson JD. *Lancet* 1991; 337: 1044–1045.
- Crossman DC, Dashwood MR, Brain SD, McEwan J, Pearson JD. *British Journal of Pharmacology* 1990; 99: 71–76.

VARIATIONS IN RESPIRATORY SINUS ARRHYTHMIA MAY REFLECT LEVELS OF ANAESTHESIA

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Respiratory sinus arrhythmia (RSA) is a non-pathological increase in heart rate with inspiration and decrease with expiration. Off-line measurements of the amplitude of RSA have shown it to decrease during isoflurane–nitrous oxide anaesthesia in man and increase during the subsequent recovery period [1]. Established on-line tests for RSA have concentrated on screening diabetics exhibiting autonomic neuropathy, the level of RSA being thought widely to reflect parasympathetic tone [2]. Some variation is present in the relation between RSA and parasympathetic tone in non-anaesthetized individuals [3].

We have studied changes in the amplitude of RSA in 60 patients undergoing elective surgery. Informed consent was obtained in accordance with a procedure approved by the local Ethics Committee. Patients were anaesthetized with a bolus i.v. dose of propofol 2 mg kg $^{-1}$ and anaesthesia was maintained with 66 % nitrous oxide in 33 % oxygen and 1–3 % isoflurane, and fentanyl 1–1.5 $\mu\text{g kg}^{-1}$. Thirty-eight patients breathed spontaneously and in 22 patients the lungs were ventilated artificially after paralysis with vecuronium or atracurium. Circular statistics [2] were used to derive the level of RSA on-line in 1-min epochs from standard ECG and respiratory waveform data using a microcomputer-based system.

In 83 % of patients where the lungs were ventilated artificially, an increase in RSA following laryngoscopy occurred while in 86 % of spontaneously breathing patients an increase in RSA after insertion of a laryngeal mask airway was present. This increase was followed usually by a decrease in RSA to values less than those seen before anaesthesia. A rapid increase and subsequent reduction in RSA to less than baseline values occurred in 100 % of paralysed and 79 % of spontaneously breathing patients after cessation of anaesthesia and up to 4 min before recovery. A possible mechanism for

this activity is firing of vagal neurones stimulated by waking arousal in the nucleus solitarius of the brainstem. On-line monitoring of RSA may, therefore, give a prediction of light anaesthesia and wakefulness in man.

REFERENCES

1. Donchin Y, Feld JM, Porges SW. *Anesthesia and Analgesia* 1985; 64: 811-815.
2. Genovely H, Pfeifer MA. *Diabetes Metabolism Reviews* 1988; 4: 255-271.
3. Kollai M, Mizsei G. *Journal of Physiology* 1990; 424: 329-342.

DOES PHYSIOTHERAPY AFFECT THE AUDITORY EVOKED POTENTIALS OF SEDATED PATIENTS IN THE INTENSIVE CARE UNIT?

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The early cortical component of the auditory evoked potential (AEP) is depressed in a dose-related manner by a variety of inhalation and i.v. anaesthetic agents and this depression is antagonized partially by surgical stimulation. The phenomenon of stimulus antagonism suggests that the AEP may indicate the depth of anaesthesia rather than acting as a simple bioassay of brain anaesthetic concentration [1]. In order to evaluate the use of AEP as a guide to depth of sedation in the intensive care unit (ICU), we have studied the effect of a standardized stimulus (physiotherapy) on AEP in 11 paralysed patients sedated with propofol and fentanyl. Ethics Committee approval was obtained and informed consent from relatives.

EEG was recorded using a Navigator system (Biologic, U.S.A.) with frontal and mastoid electrodes. Binaural 6 Hz rarefaction click stimuli of 75 dB were given and 1500 sweeps averaged for each AEP. Six consecutive bilateral AEP were collected (two before, two during and two after physiotherapy). The ICU proved to be a hostile electronic environment and careful positioning of equipment was necessary to avoid mains interference. Mean Nb latency values were 44.68 (SEM 2.41) ms, 41.03 (2.05) ms ($P < 0.05$ compared with baseline, paired t test) and 44.45 (1.89) ms before, during and after physiotherapy, respectively. Mean Nb amplitudes were 0.85 (0.38) mV, -0.82 (0.46) mV and -0.69 (0.4) mV, respectively. Mean systolic arterial blood pressure and heart rate increased by 13 mm Hg ($P < 0.05$) and 4 beat min^{-1} ($P < 0.05$), respectively, during physiotherapy compared with baseline values (paired t test).

AEP can detect the reversible arousal provoked by physiotherapy and may have some value as a monitor of depth of sedation in the ICU, particularly for paralysed patients.

REFERENCE

1. Thornton C, Konieczko K, Jones JG, Jordan C, Doré CJ, Heneghan CPH. *British Journal of Anaesthesia* 1988; 60: 372-378.

CHANGE IN END-EXPIRATORY RESPIRATORY VOLUME WITH THIOPENTONE OR PROPOFOL INDUCTION OF ANAESTHESIA

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Bergman reported a change in end-expiratory respiratory volume (Δ -EERV) when anaesthesia was induced with thiopentone [1]. He studied 11 patients, four of whom were obese. No clear relationship between obesity and volume change was found, in contrast to other studies of functional residual capacity [2, 3]. We used the method of Bergman to assess the relationship of the change in Δ -EERV to obesity and the influence of propofol and thiopentone.

After Ethics Committee approval, 47 patients without overt respiratory disease were studied before minor gynaecological surgery. Patients were allocated randomly to receive propofol or thiopentone. Height, weight and age were recorded. A mask with a wide pneumatic rim (Respironics) was applied to the face to obtain a seal with the aid of lubricating jelly (KY). After placing the head in a slightly extended position, the patients breathed from an anaesthetic circle system, modified by the substitution of a water seal bell spirometer for the reservoir bag [1]. Anaesthesia was induced with a dose sufficient to abolish response to jaw traction given over approximately 20 s.

Seven patients were excluded from analysis because of failure to maintain a mask seal or airway patency. One patient whose weight was 196% of that expected had a Δ -EERV of 1230 ml ATPS and was treated as an outlier. In three patients who received thiopentone, lung volume increased. After thiopentone, the mean decrease in volume was 195 (SD 214) ml ($n = 20$) and after propofol 296 (199) ml ($n = 19$). These values were not significantly different (Student's t test). There was no relationship between Δ -EERV and age, height and obesity (multiple linear regression). The prompt change in respiratory system volume at induction of anaesthesia is not related significantly to obesity or induction agent.

REFERENCES

1. Bergman NA. *Anesthesiology* 1982; 57: 14-17.
2. Don HF, Wahba M, Cuadrado L, Kelkar K. *Anesthesiology* 1970; 32: 521-529.
3. Darnia G, Mascheroni D, Croci M, Tarenzi L. *British Journal of Anaesthesia* 1988; 60: 574-578.

WORK OF VENTILATING HEAT AND MOISTURE EXCHANGERS

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Heat and moisture exchangers (HME) are considered to be of low resistance and therefore to add little to the work of breathing. The present study investigated the work of ventilating across HME.

A lung model for spontaneous ventilation which produced a sinusoidal respiratory waveform was used. Work of ventilation was derived using pressure and flow values measured across the HME [1]. The HME were progressively saturated

by placement downstream of a heated water bath humidifier ventilated by the lung model. This method of ventilation to and fro between humidified gas and atmosphere simulated the physiological saturation of a HME by patients in clinical use. Pressure and flow measurements were taken at 6-hourly intervals, and the work of ventilating across each HME for one respiratory cycle derived.

The work of ventilating dry HME is relatively low (range = 35–45 mJ per respiratory cycle) ($V_T = 600$ ml). This compares with the work of breathing through Magill and Bain circuits of 86–129 mJ, and 70–140 mJ per respiratory cycle ($V_T = 500$ ml), respectively [2]. The work of ventilating across HME, however, increases as they become saturated, in particular as the 24-h maximum recommended period of use is approached. At 24 h the range of work of ventilation was 81–111 mJ. This may represent a significant additional workload to some spontaneously breathing patients.

REFERENCES

- Engstrom CG, Norlander OP. *Acta Anaesthesiologica Scandinavica* 1962; 6: 49–55.
- Kay B, Beatty PCW, Healy TEJ, Accoush MEA, Calpin M. *British Journal Of Anaesthesia* 1983; 55: 1239–1246.

IMPROVED METHOD OF ACOUSTIC REFLECTION TECHNIQUE FOR UPPER AIRWAY MEASUREMENTS

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Impaired airway patency is a common hazard during sedation and anaesthesia, and may be associated with unexpected mortality [1]. Previous studies of airway obstruction in these circumstances have been restricted by the need to use invasive or potentially harmful methods such as manometry or radiography. The acoustic reflection technique allows measurement of airway size without hazard. We have modified the technique to be used during anaesthesia.

An acoustic impulse is delivered through a wave tube into the airway. Incident and reflected waves are recorded with a microphone. Analysis of the incident and reflected signals allows a profile of the impedance changes down the airway to be calculated. The cross-sectional area can be derived and presented as a plot against the distance down the airway.

The original apparatus was of limited clinical value because the equipment was cumbersome, a mixture of helium and oxygen was used and the mathematical analysis was lengthy [2]. However, by using an acoustic impulse designed specifically, an alternative lightweight source tube may be used. Measurements may be made using air rather than helium mixtures, and the deconvolution of the reflected signal is simpler. A simple flanged mouthpiece gives good signal coupling to the airway during anaesthesia and an automated valve system allows measurements to be made at chosen times during the natural breathing cycle. Analysis of measurements made at 1 Hz can be done almost in "real time".

After validation with models of known dimensions and in volunteers, we studied five patients before minor surgery. Measurements were made with the patient awake and the

head in the neutral position. Maximum area was mean 3.08 (SD 0.25) cm². After preoxygenation, anaesthesia was induced with propofol 2–3 mg kg⁻¹ i.v. With the head in the neutral position, the area was mean 1.28 (0.26) cm², and when the head was extended, the area increased to mean 1.68 (0.57) cm². This improved method of acoustic reflectometry is a practical means of investigating the upper airway in anaesthetized patients.

REFERENCES

- Caplan RA, Ward RJ, Posner K, Cheyney FW. *Anesthesiology* 1988; 68: 5–11.
- Brooks SJ, Castile RG, Glass GM, Griscom GM, Wohl MEB, Fredberg JJ. *Journal of Applied Physiology* 1984; 57: 777–787.

A PORTABLE METHOD TO ASSESS UPPER AIRWAY REACTIVITY

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The protective reflex of the larynx is evoked by chemical or mechanical stimuli via receptors thought to be located in the hypopharynx and larynx [1]. A chemical stimulus technique was described by Hoglund and Michaelsson [2] using low concentrations of ammonia vapour to test the laryngeal reflex. The vapour is introduced into the inspired air in increasing concentrations until it produces a transient closure of the vocal cords termed a "glottic stop". We have modified this original technique to allow repeated measurements using portable equipment.

Low concentrations of ammonia vapour were produced with a mixture of 3% ammonia in nitrogen and air. A two-way balloon valve (BV) allowed the mixture to be directed to the subject or passed to an absorber constructed specially without the subject being aware of the change. The circuit was calibrated using a Bruel and Kjaer Multigas analyser type 1302. The subject rested on a couch and wore blackened goggles and listened to music via a pair of headphones. A noseclip was applied and the subject was allowed to breathe through a mouthpiece via a one-way valve; the inspiratory flow was measured using a Gould pneumotachograph and recorded on a chart recorder. The deadspace from the BV to the subject was 48 ml. The BV was operated by the investigator so that the subject took one inspiration from the ammonia circuit. A glottic stop was defined as a rapid de-

TABLE IV. Mean (SD) threshold concentration of ammonia (NH₃ %) required to produce a glottic stop. A = Single measurements made on six different days; B = measurements made every 30 min for 4 h on one day

Subject	NH ₃ % A	NH ₃ % B
A	0.059 (0.016)	0.047 (0.011)
B	0.064 (0.018)	0.049 (0.007)
C	0.038 (0.015)	0.036 (0.014)
D	0.041 (0.015)	0.047 (0.012)
E	0.053 (0.013)	0.043 (0.018)
F	0.053 (0.019)	0.054 (0.015)

crease in the inspiratory flow, the flow decreasing by at least 25% of the peak inspiratory flow and followed by a swift recovery; the whole event lasted less than 0.5 s. The concentration of ammonia was increased in regular steps until the concentration required to produce a glottic stop was reached.

Six healthy, non-smoking male volunteers were studied aged 29–34 yr and weight 72–85 kg. Subjects abstained from alcohol from 12:00 the previous day. Single measurements were made on six different days and every 30 min for 4 h on one day (table IV).

This technique may be useful for assessing upper airway reactivity in both the laboratory and the clinical environment.

REFERENCES

1. Hinkle JE, Tatum KR. *Anesthesiology* 1971; 35: 634–637.
2. Hoglund NJ, Michaelsson M. *Acta Physiologica Scandinavica* 1950; 21: 169–173.

RELATIONSHIP BETWEEN PERIOPERATIVE ISCHAEMIC AND HYPOXIC EVENTS IN PATIENTS WITH CARDIOVASCULAR DISEASE

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Patients with cardiovascular disease undergoing surgery are at risk from perioperative myocardial ischaemia. Episodes of hypoxia are common in the postoperative period and may increase the risk of myocardial ischaemia. We have studied the temporal relationship between perioperative ischaemia and hypoxia.

Eleven patients with cardiovascular disease (angina, previous myocardial infarction or treated hypertension) were enrolled in the study. Each patient had continuous recording of ECG and oxygen saturation for up to 16 h before, and up to 48 h after operation. The ECG was recorded with a Compas ambulatory ECG monitor set in ST analysis mode [1]. Oxygen saturation was recorded every 6 s when the saturation was < 90% using an Ohmeda 3700 pulse oximeter interfaced with a BBC computer. The internal clocks of the Compas monitor and BBC computer were synchronized.

The time and duration of all ST and desaturation events were recorded. An ST event was defined as an episode of ST segment depression > 1 mm lasting > 30 s. A desaturation event was defined as a saturation < 90% for > 30 s. The mean saturations over the 2 min before and immediately after each ST event were measured. The total ischaemic time and desaturation time were calculated for each hour of monitoring.

Desaturation events occurred in nine patients before operation and in 10 patients after operation, and ischaemia in seven and nine patients, respectively. A total of 278 desaturation events and 237 ST events were recorded. The duration of ischaemia in each hour was correlated positively with the duration of desaturation ($P < 0.001$). Of the 278 desaturation events, 65 (23%) were associated with ischaemia. The events during which ischaemia occurred were significantly longer (mean 14.4 (range 0.5–493) min) than those with no ischaemia (5.5 (0.5–88) min) ($P = 0.046$, ANOVA). Grouping of events by the smallest recorded saturation demonstrated that ischaemia was more frequent when saturation was < 85% ($P < 0.05$, chi-square). Of the 237 ST events, 41 (17%) were

associated with desaturation. Only 24 (10%) were preceded by a saturation < 90%. The duration of ST events were correlated negatively with the minimum saturation recorded during the event ($P < 0.001$). There was no correlation between the duration of ST events and desaturation before and after an ST event or between duration of ST events and heart rate.

In this study most ischaemic events occurred without desaturation and most desaturation events without ischaemia. An associated ischaemic event was more likely to occur if the desaturation period was prolonged and if saturation was less than 85%.

REFERENCE

1. McHugh P, Parsloe M, Wyld R, Reilly CS. *British Journal of Anaesthesia* 1989; 63: 234P–235P.

DIRECT EVIDENCE FOR FREE RADICAL GENERATION IN EXPERIMENTAL LUNG INJURY

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Oxygen-derived free radicals are thought to contribute to acute lung injury although their extremely short half-lives means that there is little direct evidence of their generation in such circumstances. We have used spin trap electron spin resonance (ESR) spectroscopy to examine the production of free radicals in an *in vivo* model of acute lung injury [1].

After induction of anaesthesia in specific pathogen-free New Zealand white rabbits, the lungs were ventilated with oxygen enriched air through a tracheostomy. An experimental group ($n = 6$) received endotoxin $3 \mu\text{g kg}^{-1}$ (LPS, *E. coli* 026:B6, Sigma) i.v. in isotonic sterile saline 10 ml, whilst a control group received only sterile saline. One hour after LPS an i.v. infusion of the spin trap α -phenyl N-tert-butyl nitron (PBN) 300 mg kg^{-1} was given over 45 min. An aerosol of ^{99m}Tc -DTPA was administered after starting the infusion, and the changes in alveolar epithelial permeability measured before and after ventilation with 20, 20-ml breaths of smoke (given 2 h after LPS). Blood samples were obtained immediately before and for 30 min after ventilation with smoke and the plasma stored in liquid nitrogen before ESR analysis.

As shown previously [1], while LPS alone had no significant effect on the pulmonary clearance of ^{99m}Tc -DTPA, it amplified significantly the smoke-induced increase in epithelial permeability. Plasma ESR analysis (fig. 2) failed to demonstrate any evidence of radical generation after LPS or smoke alone. This contrasted with the LPS-pretreated group, in which smoke exposure induced a burst of radical generation (background signal noise 4–5 cm, 95% confidence intervals of difference between control and LPS groups (cm): 0.87–9.03, 2.26–7.91, 1.50–6.83, 1.03–7.37 at 1, 2, 5 and 10 min after smoke, respectively).

This direct evidence of radical generation, which is associated with functional changes in pulmonary integrity, supports the hypothesis that oxygen-derived free radicals contribute to the evolution of acute lung injury.

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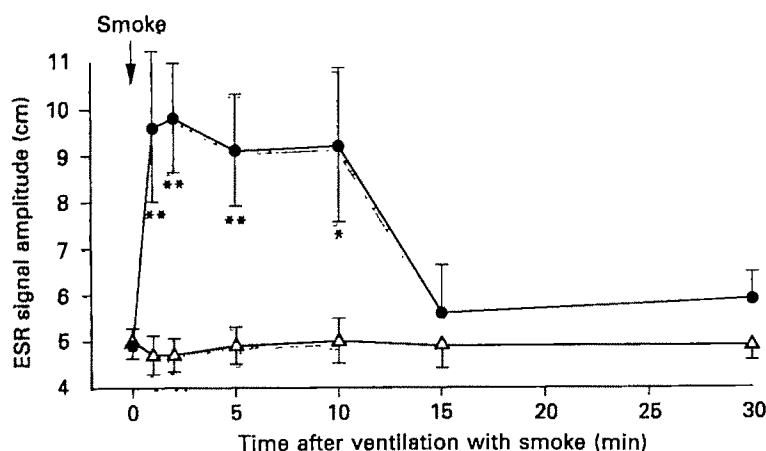


FIG. 2. Plasma ESR analysis (mean (SEM)) after ventilation with smoke in the control (Δ) and endotoxin (●) groups. * $P < 0.05$, ** $P < 0.01$.

REFERENCE

1. Murphy PG, Myers DS, Jones JG. *British Journal of Anaesthesia* 1990; 65: 578P-579P.

SPECTRAL ANALYSIS OF THE ELECTROMYOGRAM: EFFECT OF FENTANYL

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Spectral analysis of the electromyogram (EMG) has aided the differential diagnosis of neurological disease [1] and illuminated the mechanisms of neuromuscular block in anaesthesia [2]. A shift in the spectrum towards lower frequencies is a feature of fatigue, neuropathy, reduced conduction velocity and neuromuscular block. We have investigated the EMG changes that have been described after opioid administration [3].

Eleven patients (mean age 55 yr) were studied, and each was premedicated with either fentanyl and droperidol, or temazepam. Surface electrodes were placed on the ventral aspect of the forearm. The EMG of the wrist flexors was recorded during a 4-s isometric contraction. After a rest period, fentanyl $4-7.5 \mu\text{g kg}^{-1}$ was administered, and after 60 s an identical isometric contraction was recorded. The signals were stored on computer disc in the form of a digitized (1000 Hz) signal and analysed with commercially available software. The spectrum was described with reference to five variables: peak frequency (f_{max}), median peak frequency (mpf), those points representing upper and lower quartiles of amplitude (lq and uq) and area under the curve (AUC). A paired t test was used to compare the data before and after administration of fentanyl. A control group of similar age who received no premedication or fentanyl was examined also.

There was no significant difference in AUC (expressed as a ratio) between the test and control group (1.13 vs 1.008). Spectral analysis showed a shift to lower frequencies (i.e. a reduction in mpf, lq and uq) (table V). It is possible that this

TABLE V. Effect of fentanyl on the shape of the EMG spectrum. f_{max} = Peak frequency; mpf = median peak frequency; lq and uq = upper and lower quartiles of amplitude. $n = 12$ (1 patient was studied twice). Values are mean (SEM) (Hz). ** $P < 0.01$, *** $P < 0.001$

	f_{max}	mpf	lq	uq
Before fentanyl	99 (14.3)	155 (11.6)	86 (7.2)	260 (13.8)
After fentanyl	88 (15.9)	147 (12.7)	81 (7.1)	248 (16.0)
Frequency reduction	11	8**	5.4***	12.4**

is an opioid specific action but the possibility that it is a non-specific feature of sedation cannot be ruled out.

REFERENCES

1. Mills KR. *Journal of Physiology* 1982; 326: 401.
2. Harper NJN, Pugh ND, Healy TEJ, Petts HV. *British Journal of Anaesthesia* 1987; 59: 200-205.
3. Benthuyssen JL, TySmith N, Sanford J, Head N, DecSilver H. *Anesthesiology* 1986; 64: 440-446.

VIDEO SURVEILLANCE OF OXYGEN ADMINISTRATION BY MASK IN POSTOPERATIVE PATIENTS

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Patients may become hypoxaemic in the 24 h after abdominal surgery [1] and supplementary oxygen can prevent these episodes of hypoxia [2]. Oxygen by face mask is prescribed commonly but the face mask does not always remain positioned properly. In this study, overnight video surveillance was used to record mask position and the events that resulted in its

TABLE VI. Reasons for mask removal

	Mouth care	Temp. obstruction	Patient removal	Other care	Fell off	Vomit/ retch
No. times mask off	21	16	12	8	5	2

displacement. Associated changes in arterial oxygen saturation were determined by pulse oximetry.

Twenty ASA I-III patients (seven men, mean age 57.3 yr (range 39-78 yr) and mean weight 70.7 kg (range 50-95 kg) undergoing elective abdominal surgery were studied. Anaesthetic technique and postoperative analgesia were not standardized. Oxygen by Hudson face mask at 4 litre min^{-1} was prescribed for all patients after operation. Correct placement of the mask was confirmed at the start of the 8-h study period from 22:00 on the first night after operation. The nursing staff were unaware of the purpose of the study. The video camera operated in ambient light and was used to record the patient's face, oxygen mask position and time as indicated by a clock within the field of view. Arterial oxygen saturation readings were recorded on to a computer every 15 s from an Ohmeda 3700 pulse oximeter. A note was made of the dose and timing of administration of postoperative analgesia and the patient's subjective assessment of the comfort of the mask. The following were determined from review of the video recordings: the number of times the mask was removed or replaced and the associated events; the length of time for which the mask was on or off; changes in arterial oxygen saturation with alterations in mask position.

The mask remained on continuously and positioned properly in only one patient (table VI). In the other 19 patients it was removed a total of 64 times (range 1-10 times per patient) and remained off, in total, for an average of 1 h 56 min 22 s per patient (range 1 min 0 s-7 h 46 min 57 s). Mask removal resulted in an average decrease in oxygen saturation of 4% (range 0.5 to -12.5%). Average oxygen saturation with the mask on was 96 (85.9-99.6)% and with the mask off 91 (82.4-98.2)%. Oxygen saturation was $\leq 89\%$ for an average of 1 h 4 min 3 s and the mask was off for 72% of the time whereas oxygen saturation was $\geq 95\%$ for an average of 5 h 10 min 19 s and the mask was off for only 2% of this time. Two patients had an average saturation less than 95% with the mask on (85.9 and 91.2%) but these values were greater than the average values with the mask off (82.5 and 85.9%). Four patients had an average oxygen saturation $\geq 95\%$ with the mask off but in all cases the average saturation was greater still with the mask on.

Many patients prescribed continuous mask oxygen in the postoperative period will receive only intermittent therapy. In this study oxygen by mask at 4 litre min^{-1} increased oxygen saturation and maintained an average saturation $\geq 95\%$ in most but not all of the patients. To minimize postoperative hypoxaemia, improved staff education or an alternative method of oxygen administration is indicated.

REFERENCES

1. Catley DM, Thornton C, Jordan C, Lehan JR, Royston D, Jones JG. *Anesthesiology* 1985; 63: 20-28.
2. Jones JG, Jordan C, Scudder C, Rocke DA, Barrowcliffe M. *Journal of the Royal Society of Medicine* 1985; 78: 1019-1022.

MEASUREMENT OF ENERGY EXPENDITURE IN CRITICAL ILLNESS USING ^{13}C LABELLED BICARBONATE

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The measurement of energy expenditure (EE) in hospital patients is performed normally using indirect calorimetry. This is a cumbersome technique and where ventilation is controlled artificially there are problems with oxygen consumption measurement at a high $\text{F}_{\text{I}\text{O}_2}$. The use of ^{13}C -sodium bicarbonate to measure carbon dioxide production (VCO_2) and thus EE involves only an i.v. infusion and collection of expired air [1], although the technique could present problems in critically ill patients because of metabolic disturbances. Measurements of VCO_2 have been made in critically ill patients using labelled ^{13}C -sodium bicarbonate and the results compared with VCO_2 and EE measured using an Engstrom Metabolic Computer (EMC, Gambro Engstrom, Bromma, Sweden) [2].

Nine critically ill patients (ventilation controlled artificially and fed parenterally) received 99% ^{13}C -sodium bicarbonate 5 $\mu\text{mol min}^{-1}$ i.v. for 8h, (one patient on two occasions). Expired air was collected from the exit port of the ventilator (Engstrom Erica) before infusion and thereafter hourly throughout the study. VCO_2 and V_O_2 were measured continuously over the same period using the EMC.

In all patients $^{13}\text{CO}_2$ recovery had stabilized by 6 h. $^{13}\text{CO}_2$ recovery at 6-8 h was 51.7-69.8% (median 62.2%, mean 61.6%). The mean recovery was used to calculate VCO_2 from the infusion results. Mean (SD) RQ over the 8-h infusion period measured using the EMC was 0.80 (0.07) and this value was used to calculate V_O_2 and EE from the VCO_2 results of the ^{13}C -sodium bicarbonate infusion. Estimates of V_O_2 from the bicarbonate infusion differed from the EMC value by 9.5 to -13.2 (median 2.9)% and estimates of EE by -10.7 to 8.8 (median -3.7)%.

In conclusion, $^{13}\text{CO}_2$ recovery in critical illness appears to be lower than in normal individuals [1]. It is easy to institute technically by the bedside and as a means of measuring EE it appears to be comparable in accuracy to short-term indirect calorimetry measurements [3].

REFERENCES

1. Elia M, Fuller N, Murgatroyd P. *Proceedings of the Nutrition Society* 1988; 47: 247-258.
2. Regan CJ, Snowdon SL, Campbell IT. *Critical Care Medicine* 1990; 18: 871-877.
3. Green CJ, Philips B, McClelland P, Campbell IT. *Proceedings of the Nutrition Society* 1990; 49: 185A.

ENOXIMONE DURING CORONARY BYPASS SURGERY

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Pharmacological or mechanical support of the circulation is required in many patients in the period of weaning from cardio-

TABLE VII. Mean cardiac function indices before cardiopulmonary bypass (CPB), 5, 10 and 30 min after bypass, after sternal closure (Closure) and 2 h after the end of surgery (ITU). CI = Cardiac index; PCWP = pulmonary capillary wedge pressure; SVRI = systemic vascular resistance index

	Before CPB	5 min	10 min	30 min	Closure	ITU
CI (litre min ⁻¹ m ⁻²)						
Enoximone	2.29	4.12	4.44	3.84	3.29	3.81
Saline	2.20	3.07	3.58	3.26	2.88	2.64
PCWP (mm Hg)						
Enoximone	13.1	10.1	9.4	8.8	8.8	9.5
Saline	14.1	15.0	14.6	14.3	14.3	10.3
SVRI (dyn s cm ⁻⁵ m ²)						
Enoximone	3225	1142	1072	1142	1482	1494
Saline	2997	1703	1594	1549	1893	2126

pulmonary bypass. Enoximone is a phosphodiesterase inhibitor which may have a role in the management of post-bypass cardiac impairment, particularly in those patients with pre-existing cardiac dysfunction [1, 2].

Sixteen consecutive patients with cardiac ejection fraction less than 0.5 undergoing coronary bypass grafting were allocated to one of two groups. Anaesthesia was induced with fentanyl, thiopentone, pancuronium and halothane. On removal of the aortic cross-clamp, patients were given either enoximone 0.5 mg kg⁻¹ and an infusion of enoximone 10 µg kg⁻¹ min⁻¹ or saline, in a double-blind manner. After weaning from cardiopulmonary bypass, inotropic support was used at the discretion of the consultant anaesthetist. Cardiac output, systemic and pulmonary arterial pressures, left pulmonary capillary wedge pressure (PCWP) and right central venous pressure (CVP) were measured before cardiopulmonary bypass, at 5, 10 and 30 min after bypass, after sternal closure, and 2 h after the end of surgery. Cardiac index (CI) and systemic and pulmonary vascular resistance indices (SVRI and PVRI) were calculated using standard formulae.

Patients administered enoximone tended to have a higher CI and smaller PCWP and SVR values but this did not reach statistical significance (table VII). Six patients in the saline group and one in the enoximone group subsequently required inotropic support ($P = 0.04$, Fisher exact test).

REFERENCES

1. Evans DB. *American Journal of Cardiology* 1989; 63: 9A-11A.
2. Boldt J, Kling D, Zickman B, Dapper F, Hempelmann G. *British Journal of Anaesthesia* 1990; 64: 611-616.

HAEMODYNAMIC AND OXYGEN TRANSPORT EFFECTS OF ISOFLURANE AS SEDATION IN VENTILATED PATIENTS IN THE INTENSIVE CARE UNIT

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Isflurane may be a suitable alternative for sedation of ventilated patients in intensive care [1] when combined with an opiate for analgesia. Although isoflurane causes myocardial

depression in some patients in anaesthetic concentrations [2], its effect on haemodynamic and oxygen transport variables in patients with septicaemia or treated haemorrhage in sub-anaesthetic doses (< 0.6 vol %) has not been investigated.

We studied the following variables: cardiac index (CI), mean arterial pressure (MAP), left ventricular stroke work index (LVSWI), systemic vascular resistance (SVR), mean pulmonary artery pressure (PA), pulmonary vascular resistance (PVR), oxygen delivery (DO_2), and oxygen consumption (VO_2), using a pulmonary artery flotation catheter in 12 cardiovascularly stable patients with septicaemia or treated haemorrhage (mean age 53 yr, range 18-75 yr). Isoflurane was administered in a stepwise manner (0, 0.2, 0.4, 0.6 vol % isoflurane in an air, oxygen mixture). Alfentanil 2.2 µg kg⁻¹ min⁻¹ was used for analgesia. Expired carbon dioxide and inspired and expired isoflurane concentrations were monitored using a Datex Capnomac TM anaesthesia gas monitoring system. Statistical analysis was by one-way ANOVA.

Table VIII shows the results of haemodynamic and oxygen transport measurements.

We conclude that isoflurane in subanaesthetic concentrations causes mild myocardial depression with significant effects on MAP and LVSWI but little effect on DO_2 . The significant reduction in VO_2 at 0.6 vol % may be a reflection of less oxygen requirement as a result of a deeper level of sedation.

REFERENCES

1. Kong KL, Willatts SM, Prys-Roberts C. *British Medical Journal* 1989; 298: 1277-1280.
2. Priebe HJ. *Anesthesiology* 1989; 71: 960-976.

DOSE REQUIREMENTS OF NEOSTIGMINE FOR ANTAGONISM OF VECURONIUM NEUROMUSCULAR BLOCK IN THE ELDERLY: COMPARISON WITH ADULTS

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The duration of action of vecuronium is prolonged in elderly subjects [1]. It is, however, not clear if this effect has any influence on the dose requirements of neostigmine for antagonism of neuromuscular block. The present study was

TABLE VIII. Haemodynamic and oxygen transport measurements after administration of isoflurane. Values are mean (SEM). *P < 0.05; ** P < 0.01

	Isoflurane (vol %)			
	0	0.2	0.4	0.6
CI (litre min ⁻¹ m ⁻²)	4.6 (0.24)	4.9 (0.26)	4.7 (0.27)	4.3 (0.26)*
MAP (mm Hg)	90 (4.3)	83 (3.9)*	81 (4.1)*	76 (3.8)**
LVSWI (g mm ⁻²)	57 (6.4)	58 (6.4)	50 (5.6)*	45 (5.0)*
SVR (dyn s cm ⁻⁵ m ⁻²)	1397 (84)	1238 (88)*	1340 (114)	1316 (127)
PA (mm Hg)	25 (2.3)	23 (1.3)	24 (3.0)	22 (1.4)*
PVR (dyn s cm ⁻⁵ m ⁻²)	204 (29)	187 (17)	218 (31)	184 (21)
Do ₂ (ml min ⁻¹ m ⁻²)	716 (59)	759 (64)	704 (64)	660 (67)
Vo ₂ (ml min ⁻¹ m ⁻²)	151 (8.1)	151 (8.8)	139 (9.2)	136 (11.0)*

designed to assess the dose requirements of neostigmine in the elderly.

Thirty-six elderly patients aged 70 yr or more and 36 adult patients aged 18–50 yr were recruited into the study. Patients were anaesthetized with thiopentone 3–5 mg kg⁻¹, fentanyl 1–3 µg kg⁻¹, 70% nitrous oxide in oxygen and halothane 1.5 MAC (end-tidal), and the lungs ventilated to normocarbida. The ulnar nerve was stimulated at the wrist with supra-maximal stimuli of 0.2 ms duration, in a train-of-four (TOF) mode at 2 Hz every 10 s and the force of contraction of the adductor pollicis measured and recorded.

After stabilization of control responses, patients received vecuronium 0.08 mg kg⁻¹ as a single bolus and the time to recovery of the first response in the TOF (T1) to 10% of control value was noted. At this point six patients in each of the two age groups were allocated randomly to receive neostigmine 5, 15, 25, 35 or 45 µg kg⁻¹, or saline, all made up to a volume of 5 ml. TOF responses were recorded continuously over the next 10 min. The study was terminated at this stage and more neostigmine administered and/or ventilation continued until satisfactory recovery. Dose-response curves were constructed after linear regression of the arcsine transformation of the response on the log of the dose and the estimated dose of neostigmine to produce a TOF of 70% (ED₇₀-TOF) at 5, 7 and 10 min calculated.

The results are summarized in table IX. Time for the return of T1 to 10% was longer in the elderly subjects (P < 0.05). The ED₇₀-TOF was significantly greater at all times in the elderly compared with the adult patients (P < 0.05). The dose requirements of neostigmine decreased in both

groups if more time was allowed for antagonism of block, suggesting the importance of concurrent spontaneous recovery from a vecuronium-induced block during antagonism with neostigmine. The requirement of more neostigmine in the elderly may be the result of a slower spontaneous recovery from vecuronium in this age group.

REFERENCE

1. d'Hollander A, Massaux F, Nevelsteen M, Agoston S. *British Journal of Anaesthesia* 1982; 54: 653–657.

USE OF MIVACURIUM CHLORIDE BY CONSTANT INFUSION IN THE ANEPHRIC PATIENT

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The new short-acting non-depolarizing neuromuscular blocking agent, mivacurium, is thought to be metabolized by plasma cholinesterase [1]. Thus clearance from the body should be independent of the kidney. We compared the pharmacodynamic effects of this drug in anephric patients with a healthy control group.

Ten anephric and 10 healthy patients with normal renal function were studied. In each patient, pseudocholinesterase activity and dibucaine number were checked before operation. The patients were premedicated with diazepam 10 mg orally. Anaesthesia was induced with midazolam 0.05 mg kg⁻¹, fentanyl 1.0–2.0 µg kg⁻¹ and thiopentone 3.0–5.0 mg kg⁻¹ and maintained with 70% nitrous oxide in oxygen whilst two i.v. infusions were established in one arm and electromyographic (EMG) monitoring in the other, using a Medelec MS6 and train-of-four (TOF) stimuli to the ulnar nerve at the wrist. After control readings of TOF had been obtained, mivacurium 0.15 mg kg⁻¹ was administered into a dedicated infusion. When the first of the TOF (T1), had returned to 5% control (TO), a constant infusion of mivacurium 10 µg kg⁻¹ min⁻¹ was started. Increments of midazolam and fentanyl were given as indicated clinically. The height of T1/TO was measured every 3 min and the infusion rate adjusted in 1-µg kg⁻¹ min⁻¹ increments to maintain T1/TO = 5%. At the end of surgery the mivacurium infusion was discontinued and when T1/TO had reached 20%, neostigmine 0.035 mg kg⁻¹ and atropine 0.015 mg kg⁻¹ were administered. TOF monitoring was continued until T1/TO and the TOF

TABLE IX. Dose requirements of neostigmine (mean (SD) [95% confidence limits]). *P < 0.05 compared with adult patients

	Adult patients	Elderly patients
n	36	36
Age (yr)	32 (11)	78 (6)
Time to 10% recovery of T1 (min)	24 (5.5)	33 (7.8)*
ED ₇₀ -TOF (µg kg ⁻¹)		
5 min	41 [31–56]	58 [44–75]*
7 min	30 [23–38]	42 [34–52]*
10 min	19 [14–25]	31 [26–37]*

TABLE X. Mean (SD) pharmacodynamic recovery data in anephric and healthy subjects. * $P < 0.05$; ** $P < 0.01$

	Anephric subjects	Healthy subjects
5% T1/TO (min)	14.9 (7.6)	9.3 (2.7)*
Infusion rate ($\mu\text{g kg}^{-1} \text{min}^{-1}$)	6.0 (1.1)	10.5 (2.0)**
20% T1/TO (min)	7.4 (4.4)	9.0 (4.3)
75% T1/TO (min)	5.5 (3.1)	5.4 (2.7)
70% T4/T1 (min)	5.6 (2.9)	8.2 (4.0)

ratio (T4/T1), had reached 75% and 70%, respectively. Variables in the two groups were compared using the Mann-Whitney *U* test.

There was no significant difference between the two groups in the maximum block achieved after administration of the bolus dose of mivacurium, or in the time to maximum block (table X).

The mean pseudocholinesterase activity in the anephric group was 608 (range 379–894) iu litre⁻¹ and in the healthy group, 682 (range 527–998) iu litre⁻¹ (ns).

Patients in chronic renal failure may be more sensitive to mivacurium, possibly as a result of an acquired decrease in plasma pseudocholinesterase although decreased renal clearance cannot be ruled out.

ACKNOWLEDGEMENT

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REFERENCE

1. Savarese JJ, Ali HH, Basta SJ. *Anesthesiology* 1988; 68: 723–732.

AN IN VIVO PHARMACODYNAMIC MODEL FOR STUDYING THE EFFECTS OF MUSCLE RELAXANTS ON VOCAL CORD MOVEMENTS

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ANALYSIS OF THE SHAPE OF THE LARYNGOSCOPE BLADE

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In 1944 Macintosh wrote: "the precise shape or curve of the blade does not seem to matter much provided the tip does not go beyond the epiglottis" [1]. This question does not appear to have been studied systematically. Normal laryngoscopy requires forward displacement of the hyoid by the tip of the laryngoscope blade [2]. A mathematical model describing intubation suggests that optimum view depends on appropriate head and neck positioning and also having the mouth closed around the blade [3]. In figure 3, I represents the tip of the upper incisors and T a point just above the vocal cords where the tip of the blade should lie. In an optimal situation, point

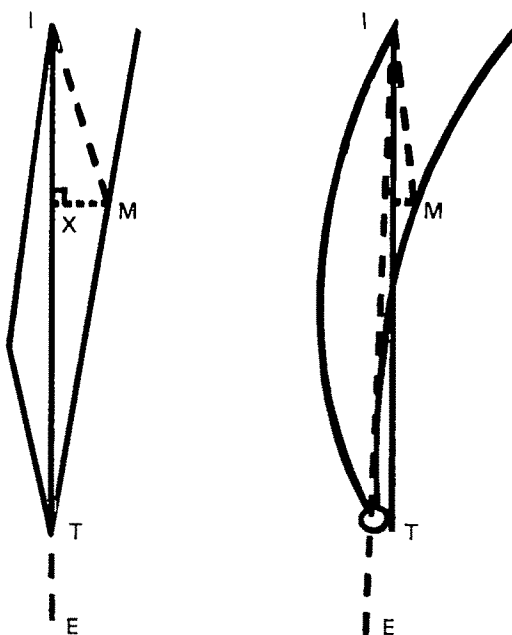


FIG. 3. Relevant angular measurements for idealized straight and curved blades. The incisor surface of each blade is to the left. EIT, the eyeline angle, may be zero (as shown for the straight blade) or positive. MIT may be either positive or negative depending on whether M is to the right or left of IT. (See text for explanation of reference points.)

X on IT lies opposite the midpoint of the mandible and $XT/IT = 2/3$; M lies on a perpendicular from X at the tongue surface of the blade. Angle EIT is a measure of eyeline displacement and MIT reflects that part of the blade which appears to encroach on the forward space immediately behind the mandible. (This space is an important limiting factor in difficult laryngoscopy.)

Accurate drawings of standard laryngoscope blades were made and checked until faithful reproductions were confirmed. From these images variations in angles EIT and MIT were studied relative to depth of blade insertion by keeping T constant and changing IT to different positions for I along the incisor surface of the blade.

With straight blades, the eyeline angle BIT remains small, but beyond a certain depth of insertion, the curved blade eyeline angle increases progressively. MIT remains positive for straight blades while a curved shape allows MIT to become negative in the clinically important regions. This effectively increases the forward space and counters the adverse effect of the curve on the eyeline.

Our work indicates the relevance of the shape of the laryngoscope blade and how blades may be compared.

REFERENCES

1. Macintosh RR. *Lancet* 1944; 1: 485.
2. Horton WA, Fahy L, Charters P. *British Journal of Anaesthesia* 1989; 63: 435–438.
3. Horton WA, Fahy L, Charters P. *British Journal of Anaesthesia* 1990; 65: 583P–584P.

GASTRO-OESOPHAGEAL REFLUX AND TRACHEO-BRONCHIAL CONTAMINATION IN THE INTENSIVE CARE UNIT

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The presence of a cuffed tracheal tube does not guarantee protection of the airway from gastro-oesophageal reflux [1]. Previous studies using dyes have evaluated the incidence of passage of fluid material from the pharynx into the trachea in the presence of a cuffed tube. These studies were subject to certain limitations. The evaluation was intermittent and did not take into consideration *in vivo* events such as vomiting or silent reflux, and did not give any indication of the pH of the material aspirated [2]. We studied patients in the intensive care unit (ITU) whose tracheas were intubated for a minimum of 24 h, using methods which allowed simultaneous measurement of oesophageal and tracheal pH in a continuous fashion.

After local Ethics Committee approval and informed consent were obtained, 20 patients whose tracheas were intubated orally were studied in the ITU. Oesophageal and tracheal pH were measured simultaneously and continuously using fine probes with antimony electrode tips connected to a Digi-trapper (Synectics, Sweden) [3], which recorded the pH values for subsequent computer analysis. The tracheal probe was passed in a specially prepared tracheal tube so that the tip of the probe projected 1.5 cm from the tip of the tube. The oesophageal probe was passed nasally into the stomach and withdrawn so that the tip was 30 cm from the anterior nares.

Continuous pH monitoring on both channels was carried out for an average of 20 h in the ITU, during which time other events such as position changes, suctioning and drug administration were noted also. Tracheal cuff pressures were measured every 2 h. Patient follow-up continued for 5 days for evidence of pulmonary complications.

Significant episodes of gastro-oesophageal reflux (pH 4) were recorded in 11 patients (55%). Significant tracheal acid contamination occurred in six patients (30%), and four of these went on to develop pulmonary complications. Cuff pressures were in the recommended range in five of six patients who developed acid tracheal contamination.

Patients in the study received medications aimed at preventing stress ulceration, at the discretion of the treating physician. Eleven patients received sucralfate, five received histamine H₂ antagonists and four had no treatment. Five of the six patients with tracheal contamination were in the sucralfate group, whereas none of the patients receiving H₂ antagonists and one of the non-treated group had tracheal contamination.

This study showed that gastro-oesophageal reflux is a frequent occurrence in ITU patients and that the presence of a cuffed tracheal tube does not guarantee protection of the lungs from acid contamination. Furthermore, tracheal contamination is associated with a high incidence of pulmonary complications. Drugs used to modify gastric pH may influence the incidence and severity of these episodes.

REFERENCES

1. Pavlin EG, Van Nunwegan D, Hornbein TF. *Anesthesiology* 1975; 42: 216-219.

2. Turndorf H, Rodif ID, Clarke TS. *Anesthesia and Analgesia* 1974; 53: 700-703.
3. Benson P, Mannion E, Stewart R, Burn P, McShane AJ. *British Journal of Anaesthesia* 1990; 65: 582P.

CUFFED TRACHEAL TUBES FOR PAEDIATRIC CARDIAC SURGERY CAUSE A LOW INCIDENCE OF POSTOPERATIVE AIRWAY PROBLEMS

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The use of cuffed tracheal tubes in paediatric anaesthesia is considered to be inadvisable. The principal concern is that cuffed tubes may damage the tracheal mucosa, causing swelling after extubation [1], and possibly stricture in the long term. However, the use of cuffed tubes during controlled ventilation allows monitoring of expired gas volumes, airway pressures and expired carbon dioxide which is particularly important during paediatric heart surgery. It also eliminates leaks when airway pressures are high. We present a retrospective review of post-extubational events in 304 children undergoing 330 elective cardiac operations at this hospital during the period 1986-1990.

We examined the intensive care unit records of all children younger than 5 yr admitted to the cardiac surgical intensive care unit; the trachea was intubated with Mallinckrodt (chiefly) or Portex cuffed tubes in all patients. The duration of intubation and occurrence of post-extubational airway problems were noted.

Two hundred and twenty-five children were younger than 1 yr, 56 were 1-2 yr, and 49 were 2-4 yr. Steroids were administered before extubation in 50% of cases. The trachea was intubated for less than 24 h in 231 children (67%), for 24-48 h in 78 (26%), for 48-72 h in 12 (4%), and for longer in nine (3%); the maximum was 16 days for one child.

Transient post-extubational stridor not requiring reintubation was noted in 10 children (3%). In 13 children the trachea was reintubated because of cardiac or respiratory failure, or aspiration while feeding. Only two children (0.3%) needed reintubation because of upper airway problems, but the trachea was extubated successfully the same day.

No upper airway problems suspected of being associated with previous intubation have been seen by either of the two University ENT departments in this region, or by the regional paediatric cardiologists responsible for follow-up in any of these children.

Our survey suggests that using cuffed tracheal tubes in paediatric cardiac surgery is not associated with clinical airway damage. There are several reasons for using cuffed tubes in paediatric cardiac surgery; improved monitoring, guaranteed ventilation, and the ability to use positive end-expired pressure. Their chief drawback is the need to choose a slightly smaller tube than with uncuffed tubes, which makes tracheal suction more difficult.

REFERENCE

1. Ryan TF, Todres ID, Cote CJ, Goudsouzian NG. *A Practice of Anaesthesia for Infants and Children*. London: Grune & Stratton, 1986.

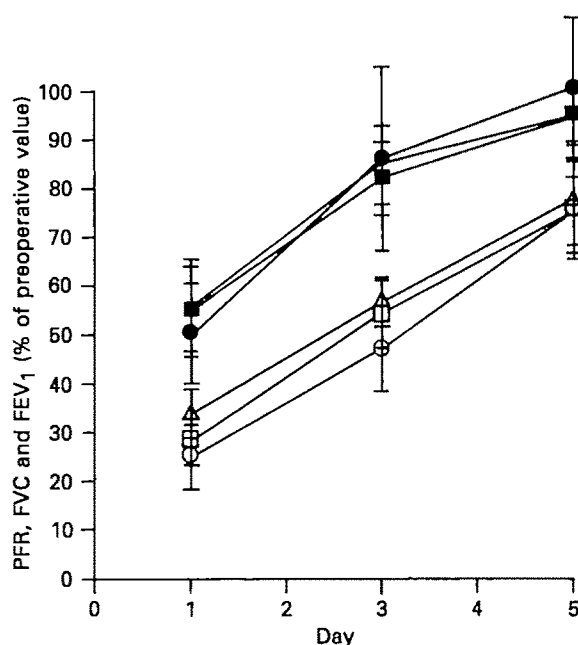


FIG. 4. Mean changes and 95 % confidence intervals in PFR (●, ○), FVC (▲, △) and FEV₁ (■, □) for the whole study period expressed as a percentage of the preoperative value. Closed symbols = treatment group; open symbols = placebo group.

POSTOPERATIVE ANALGESIA BY INFUSION OF LOCAL ANAESTHETIC INTO THE RECTUS SHEATH

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Upper abdominal surgery is associated with postoperative pneumonia [1]. Therefore it is important to minimize the deterioration in respiratory function that occurs after operation. The technique of "rectus block" has been described previously [2]. One of the authors (I.F.) has used this technique successfully in patients undergoing surgery via an upper-midline incision, obviating the use of i.m. opioids for up to 8 h after surgery. Therefore, we performed a double-blind randomized trial of continuous rectus sheath block (CRSB).

After Ethics Committee approval, 20 patients undergoing elective surgery via an upper-midline abdominal incision gave informed consent to the study. At the end of the surgical procedure an extradural catheter was introduced into the posterior aspect of each rectus sheath. The patients received bilateral rectus sheath infusions of either 0.9 % saline or 0.1 % bupivacaine in 0.9 % saline after operation, at a total rate of 42 ml h⁻¹ for a period of 72 h. Analgesia was assessed by consumption of morphine delivered by a patient-controlled analgesia system. The patients were assessed before operation and at 24, 72 and 120 h after surgery for FEV₁, FVC, PFR and a composite "co-operation with physiotherapy" score.

Data on respiratory function and total morphine usage over the first 72-h period before operation were analysed by unpaired *t* test. The postoperative FVC, FEV₁ and PFR data were expressed as percentages of preoperative values. FVC, FEV₁ and PFR data were analysed by repeated measures ANOVA in SPSS. Values from each set of postoperative observations were subjected by group to an unpaired *t* test. The overall physiotherapy score data were analysed using the Mann-Whitney *U* test.

There were no significant differences in patient characteristics or preoperative measurements between the groups. There was a significantly smaller morphine requirement over the 3-day period in the treatment group (mean 40.5 (SD 12.2) mg and 108.4 (23.7) mg). The 95 % confidence interval for the difference ranged from 50.2 to 85.5 mg (*P* < 0.0001). FVC, FEV₁ and PFR showed significantly less impairment of respiratory function in the treatment group for the study period as a whole (ANOVA, all values *P* < 0.001) and at each individual assessment (*t* test, all values *P* < 0.01) (fig. 4). The treatment group had a significantly better co-operation with physiotherapy score at 24 h after surgery (*P* < 0.05).

The technique of CRSB provides continuous analgesia from the immediate postoperative period onwards. It was not associated with untoward effects on arterial pressure and it ameliorates significantly the decrease in respiratory function that occurs in the postoperative period, an improvement which persists for 2 days after cessation of the infusion.

REFERENCES

- Garibaldi RA, Britt MR, Coleman ML. *American Journal of Medicine* 1981; 70: 677-680.
- Bryce-Smith R. Local analgesia of the trunk. In: Lee JA, Bryce-Smith R, eds. *Practical Regional Analgesia*. Amsterdam: American Elsevier, 1976; 93-95.

PAIN RELIEF AND HYPOXAEMIA DURING ADMINISTRATION OF EXTRADURAL FENTANYL BY THREE DIFFERENT METHODS

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Postoperative hypoxaemia is well documented although the effects of different methods of administration of analgesic have not been fully evaluated [1]. We examined the clinical efficacy and potential adverse respiratory effects of three different methods of administration of extradural fentanyl after elective upper abdominal surgery.

Patients gave informed consent and were allocated randomly to receive a fixed-rate infusion of fentanyl 50 µg h⁻¹ plus nurse supplemented boluses of 25 µg PRN (group 1, *n* = 15), patient-controlled analgesia (PCA) with fentanyl 25 µg demand dose and a 15-min lockout interval (group 2, *n* = 11) or PCA (as for group 2) supplementing an infusion of fentanyl 50 µg h⁻¹ (group 3, *n* = 16). All patients had continuous pulse oximetry (Sp_{o2} logged to a computer every 10 s) for 48 h. In addition, pain and sedation scores and unstimulated ventilatory frequency were measured hourly. Groups were compared by Kruskal-Wallis tests and associations examined by Spearman's rank correlation. The Wilcoxon signed rank test was used for paired data.

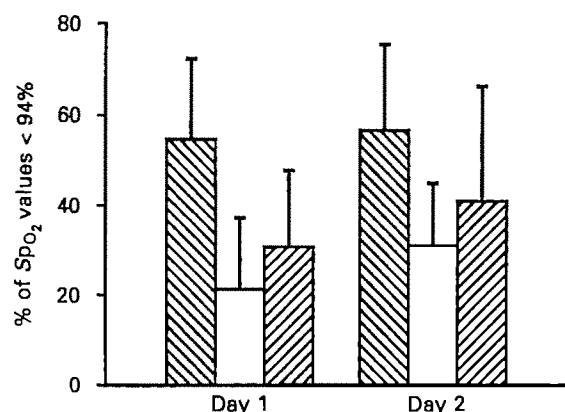


FIG. 5. Mean and 95% confidence intervals of percentage of oxygen saturation (Sp_{O_2}) values less than 94% on days 1 and 2 in group 1 (■), group 2 (□) and group 3 (▨).

There was no difference between the groups in mean age, weight, height and type of surgery. Group 2 received significantly less fentanyl (mean 1865 $\mu\text{g}/48\text{ h}$) than group 1 (2607 μg) and group 3 (3104 μg) ($P < 0.05$), although there were no significant differences in the sedation or pain scores among the three groups. Significantly greater desaturation (% time below 94%) was observed in group 1 on day 1 than groups 2 and 3 ($P < 0.05$), although there was no correlation between mean Sp_{O_2} and dose of fentanyl. Finally, hypoxaemia was significantly worse on day 2 compared with day 1 in all groups ($P < 0.05$) (fig. 5).

Despite very different dose rates, the three techniques of administration of extradural fentanyl provided comparable analgesia, although supplementation of an infusion with boluses administered by nurses led to the highest incidence of hypoxaemia. The failure to demonstrate an association between dose of fentanyl and mean Sp_{O_2} , worsening of Sp_{O_2} values on day 2 and lack of difference in Sp_{O_2} on day 2 among the three groups may suggest factors other than extradural fentanyl analgesia make a more significant contribution to postoperative hypoxaemia.

REFERENCE

1. Jones JG, Sapsford DJ, Wheatley RG. *Anaesthesia* 1990; 45: 566-573.

PHARMACOKINETICS OF ALFENTANIL IN BURNS PATIENTS

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The disposition of drugs may be altered following a thermal injury as a result of changes in binding capacity and volume of distribution. These are caused by changes in plasma protein concentrations after a burns injury including a fall in plasma albumin and an increase in acute phase reactant proteins such as α_1 -acid-glycoprotein (AAG) [1]. Alfentanil is bound highly to plasma proteins (> 90%), mainly to AAG [2]. The disposition of alfentanil in burns patients has not been described.

After Ethics Committee approval and written informed

TABLE XI. Pharmacokinetic variables in the burns and control groups. Mean (SEM)

	Burns group	Control group	P value
AAG (mg dl^{-1})	186 (10)	94 (9)	0.004
% of bound alfentanil	94.2 (0.5)	90.7 (0.4)	0.004
Cl (ml min^{-1})	125 (32)	256 (12)	0.005
V^* (litre)	12.5 (0.8)	23.8 (1.3)	0.001
T_1 (min)	305 (50)	191 (11)	0.074
Cl_{fu} (ml min^{-1})	21.6 (8)	29.3 (3)	0.07

consent, the disposition of alfentanil was studied in six patients with burns injuries (10-30% full thickness burns sustained 5-20 days previously) undergoing debridement and grafting, and six control patients, matched for age, sex and weight, undergoing elective body surface surgery. All patients received temazepam 20 mg orally 1 h before surgery. Anaesthesia was induced with thiopentone and muscle relaxation was achieved with vecuronium 0.1 mg kg^{-1} . The trachea was intubated and the lungs ventilated with 66% nitrous oxide and 0.5-1% isoflurane in oxygen. ECG, oxygen saturation and end-tidal carbon dioxide were measured continuously and arterial pressure (non-invasive) every 3 min. After induction, a bolus dose of alfentanil 50 $\mu\text{g kg}^{-1}$ i.v. was administered. Blood samples for measurement of plasma concentrations of alfentanil were obtained at 0, 2, 5, 10, 15, 30, 60 and 90 min, and at 2, 3, 4, 6, 7 and 8 h and for AAG concentration and binding at 0, 1 and 8 h. The pharmacokinetic variables were calculated using a non-compartmental model to derive AUC, AUMC, clearance (Cl), V^* and elimination half-life (T_1). Data were analysed using ANOVA (SPSSX PC) and $P < 0.05$ was taken as significant.

The burns patients had significantly greater concentrations of AAG and significantly smaller concentrations of albumin. The percentage of bound alfentanil was significantly greater in the burns group. Total Cl and V^* were decreased in the burns group ($P < 0.05$) (table XI). Clearance of the unbound fraction (Cl_{fu}) was not decreased significantly.

REFERENCES

1. Bloodlow DC, Hansbrough JF, Hardin T, Simons M. *Journal of Clinical Pharmacology* 1988; 26: 147-151.
2. Meuldermans W, Hurkmans R, Heykants J. *Archives Internationales Pharmacodynamie et de Therapie* 1982; 257: 4-19.

PATIENT-CONTROLLED ANXIOLYSIS WITH PROPOFOL

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To avoid excessive postoperative sedation and possibly delayed discharge from hospital, it is common practice not to offer anxiolytic premedication to day surgery patients. However, a significant number of these patients would like to receive anxiolytic therapy [1].

Successful use of a patient-controlled analgesia (PCA) sys-

TABLE XII. Mean (SD) anxiety (LASanx), sedation (LASsed) and affect adjective checklist (MAACL) scores and cumulative number of boluses of drug delivered and demands made in the propofol and placebo groups as assessed by the patient (P) and investigator (I), 0, 15 and 30 min before induction of anaesthesia. * $P < 0.05$

	MAACL	LASanx		LASsed		Cumulative boluses	Cumulative demands
		P	I	P	I		
Propofol ($n = 20$)							
0 min	23.8 (2.9)	67.6 (18.0)	58.3 (20.7)	15.5 (22.1)	3.9 (5.1)	—	—
15 min	15.2 (5.6)*	42.9 (19.1)*	37.5 (16.9)	41.8 (24.9)*	12.4 (17.0)	2.1 (1.0)	3.5 (5.2)
30 min	13.2 (5.7)*	36.2 (26.8)*	28.9 (17.0)	49.7 (27.7)*	15.5 (16.3)	3.6 (1.7)	5.5 (6.8)
Placebo ($n = 20$)							
0 min	22.4 (4.5)	50.5 (21.0)	52.6 (18.7)	16.7 (20.3)	4.1 (6.2)	—	—
15 min	18.3 (4.8)*	39.2 (19.1)*	39.2 (20.6)	24.0 (23.6)*	10.0 (12.7)	1.9 (0.9)	2.9 (2.9)
30 min	17.6 (5.5)*	39.2 (22.4)*	35.6 (24.1)	30.4 (27.5)*	13.4 (16.7)	3.1 (1.3)	4.6 (4.5)

tem using diazepam to provide preoperative anxiolysis has been described [2]. Following preliminary observation of the effects of very small doses of propofol, we postulated that this drug, administered to day surgery patients using a PCA system, may provide useful anxiolysis without increasing post-operative sedation.

After Ethics Committee approval, 40 female patients undergoing elective laparoscopic procedures were enrolled in a double-blind study. Patients were allocated randomly to receive either propofol 10 mg ml⁻¹ or placebo (10% Intralipid) from a PCA system programmed to deliver 1-ml boluses with a 3 or 5 min lockout period. Patients were invited to "administer the medicine until you feel no anxiety about your operation". A 100-mm linear analogue scale was completed by the patient and one investigator to assess anxiety (LASanx) and sedation (LASsed). A modified affect adjective checklist (MAACL) was used also. These tests were repeated at 15-min intervals for a minimum of 30 min before induction of anaesthesia. Number of boluses of drug delivered and demands made were recorded. Heart rate and arterial oxygen saturation were monitored and recorded continuously, and an anaesthetist was present throughout. Patients were requested to complete and return a questionnaire on the following day.

Oxygen saturation remained above 95% in all patients. The propofol group showed significantly greater reductions ($P < 0.05$, Mann-Whitney U test) in patient MAACL and LASanx scores at 15 and 30 min when compared with placebo (table XII). Increase in patient sedation scores was also significantly greater in the propofol group. These differences were not detected by the investigator scores. There was little difference in the number of boluses administered. In the post-operative questionnaire, 11 of 17 patients indicated they had benefited greatly from the PCA premedication in the propofol group compared with 4 of 14 returns in the placebo group.

Patient-controlled anxiolysis with propofol is an effective premedication technique for use in anxious patients presenting for day surgery.

ACKNOWLEDGEMENTS

We are grateful to Nellcor for loan of oximeter, Graseby and Abbott for loan of PCA systems and J. W. Sear for statistical advice.

REFERENCES

1. Mackenzie JW. *Anaesthesia* 1989; 44: 437-440.

2. Galletly DC, Short TG, Forrest P. *Anaesthesia and Intensive Care* 1989; 17: 144-150.

POSTER PRESENTATIONS

A NEW PERSPECTIVE ON INTRAOPERATIVE MONITORING OF EEG

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The compressed spectral array (CSA) has been used extensively to depict changes in EEG with different levels of anaesthesia [1]. The three-dimensional display of the CSA may present problems with visualization of trends, since the most recent time slices may obscure earlier slices.

We have developed a new representation of the CSA, linking regions of equivalent power by contours. This method of presentation has several advantages: the plot is in two dimensions, so no points are obscured as a result of inappropriate viewing angles or scales, and processing is simple, since algorithms for hidden line removal are not required.

Discontinuities in the EEG record appear as closely packed contours, alerting the anaesthetist to a change in EEG profile. Appropriate shading may also be applied to the contour map, effectively highlighting alpha, beta and delta activity.

REFERENCE

1. Pichmayer I. *EEG Atlas for Anaesthesiologists*. Berlin: Springer-Verlag, 1987.

COMPARISON OF THE EFFECTS OF ANAESTHETIC AGENTS ON MITOGEN-INDUCED LYMPHOCYTE PROLIFERATION *IN VITRO*

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Anaesthetic agents may have a short-lived and reversible effect on the immune system [1]. However, in the intensive

care unit (ICU) these effects may be more important as the agents are administered continuously to patients whose immune system may be compromised already.

Lymphocyte proliferation in response to an antigenic stimulus is an important function of the immune system. We have examined the effect of propofol and midazolam on mitogen-induced lymphocyte proliferation *in vitro*. Thiopentone was included for comparison as it is known to inhibit various immune functions [2]. Propofol is solubilized in a substance similar to 10% Intralipid, which can itself affect white cell function [3]. Therefore, the effect of 10% Intralipid alone was examined also.

Peripheral blood was obtained from healthy individuals, sedimented on Dextran and the buffy coat centrifuged on Lymphoprep to obtain a lymphocyte-rich cell layer. Lymphocyte proliferation was measured by [³H]-thymidine uptake for 6 h in cell cultures stimulated with standard mitogen preparations, in the presence or absence of varying concentrations of the agents, for 3 or 6 days.

Both propofol and thiopentone inhibited mitogen-induced proliferation (mean (SD) inhibition 68 (14.2)% and 100 (0.1)%, respectively) at 10 times the plasma concentration required for anaesthesia. At plasma concentrations required for anaesthesia (propofol 6 µg ml⁻¹, thiopentone 40 µg ml⁻¹), inhibition was -8 (3.6)% for propofol and 63 (3.2)% for thiopentone. At plasma concentrations required to produce sedation (propofol 3 µg ml⁻¹, midazolam 1.2 µg ml⁻¹), propofol produced greater inhibition than midazolam (18 (5.7)% and -6.5 (2.8)%, respectively). At 10 times this plasma concentration, inhibition was 30 (2.3)% for propofol and 55 (5.7)% for midazolam.

Intralipid, at the concentration used to carry 60 µg ml⁻¹ of propofol (i.e. 6 µl ml⁻¹) inhibited proliferation, but to a lesser extent than propofol (74 (6.7)% for propofol, 41 (2.7)% for Intralipid). At smaller concentrations of Intralipid no inhibition was observed.

In conclusion, propofol, unlike thiopentone, does not inhibit lymphocyte proliferation to mitogen *in vitro* at the plasma concentrations required for anaesthesia. However, propofol was more inhibitory at plasma concentrations required for sedation, while midazolam had no inhibitory effect at this concentration.

REFERENCES

1. Moudgil GC. *Canadian Anaesthetic Society Journal* 1986; 33: S54-S60.
2. Salo M. *British Journal of Anaesthesia* 1989; 63: 716-720.
3. Fraser I, Neoptolemos J, Woods P, Bowry V, Bell PRF. *Clinical Nutrition* 1983; 2: 37-40.

PREANAESTHETIC MEDICATION: COMPARISON OF THREE DRUG GROUPS

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Preanaesthetic medication is often used to provide pre-operative anxiolysis and sedation and a variety of agents are available. The benzodiazepines, with both sedative and anxiolytic properties are used widely. Recently it has been suggested that alpha-2 adrenergic agonists [1], and beta-blockers may be of benefit [2]. We compared the effects of oral timolol

10 mg, temazepam 20 mg, clonidine 0.2 mg, and a placebo as premedications.

After Ethics Committee approval and informed consent, healthy adults aged 18-65 yr, undergoing minor surgery were included. Baseline values for anxiety (visual analogue scale, VAS) critical flicker frequency (CFF) and a Trieger test were obtained before operation. Oral premedication was given 60-90 min before operation, in a double-blind, randomized manner. In the anaesthetic room, sedation and anxiety scores were assessed. Anaesthesia was induced with propofol to loss of response to command and maintained with 1-1.5% isoflurane in nitrous oxide and oxygen. Induction was graded on a four-point scale. Heart rate (HR) and arterial pressure (AP) were monitored routinely. After operation, recovery time was noted and VAS scores for pain and CFF readings were recorded at 30, 60 and 90 min, and a Trieger test performed at 30 min. Data were analysed using ANOVA, Student's *t* test and Mann-Whitney *U* test.

One hundred patients were studied in four equal groups. Sedation scores were similar in all groups. Anxiety was significantly less in the temazepam, clonidine and timolol groups compared with placebo (*P* < 0.05), with no significant differences between the active treatments. Propofol requirements were smaller in all three active treatment groups (*P* < 0.05), and the induction of anaesthesia was smoother. During operation, HR and AP were smallest in the timolol group compared with baseline values, but no clinical hypotension occurred. Time to eye opening and orientation was shorter in the timolol and placebo groups. The CFF values were slowest to return to baseline in the clonidine group but there were no differences between the groups by 90 min. Pain scores were lower in the clonidine and temazepam groups compared with the timolol and placebo groups in the early postoperative period. The incidence of side effects was similar in all groups.

Despite the anxiolytic properties of clonidine and the rapid recovery with timolol, in this study, neither drug offered significant advantages over temazepam. Because of the slower recovery with clonidine and the cardiovascular changes following timolol, it is unlikely that either drug be recommended for routine premedication.

REFERENCES

1. Maze M. *Journal of Clinical Anaesthesia* 1988; 1: 146-157.
2. MacKenzie W, Bird J. *British Medical Journal* 1989; 298: 363-364.

MEASUREMENT OF PROPOFOL METABOLITES IN HUMAN URINE USING NUCLEAR MAGNETIC RESONANCE

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The clearance of propofol by metabolism to water soluble conjugates which are eliminated by the kidneys (< 2% in faeces) has been studied in volunteers administered a subanaesthetic dose of ¹⁴C-labelled propofol [1]. In the present study, nuclear magnetic resonance (NMR) has been used to quantify the metabolites of propofol in human urine.

After Ethics Committee approval and patient informed consent, urine samples (0-4 h) were obtained from patients

(four male, 11 female) who had received an induction dose of propofol, and in some patients, additional doses of propofol (range 2–14 mg kg⁻¹, mean (SEM) 4.2 (0.8) mg kg⁻¹) as part of the anaesthetic for elective body surface surgery. Metabolites were concentrated by solid phase extraction using a Bond Elut C18 column and redissolved in deuterated DMSO containing maleic acid before NMR measurement in a Bruker AM 400 MHz spectrometer. Metabolites were resolved according to the disposition of C-H protons about the aromatic ring, as shown previously for samples isolated from the urine of volunteers [1], and quantified by "integral under the peak" measurements with reference to the two C-H protons in maleic acid. In addition, for the glucuronide metabolites, quantification was possible by consideration of the anomeric C-H protons of the glucuronic acid moiety. As well as substantiating values based on the aromatic region, this was necessary where paracetamol was co-administered to patients, as a result of interference in the aromatic region of the NMR spectrum. No obvious interference was evident with other co-administered drugs *vis* temazepam, fentanyl, alfentanil, atracurium, vecuronium, atropine, glycopyrrolate and neostigmine.

Urine collected up to 4 h after administration of propofol from patients undergoing elective body surface surgery without i.v. fluids, contained the following: 1-quinol glucuronide (mean (SEM) of the administered dose 4 (1)%), 4-quinol glucuronide (4 (0)%), propofol glucuronide (17 (1)%) and 4-quinol sulphate (1 (0)%). The smaller proportion of the dose excreted in the urine of these patients compared to volunteers [1] may be attributed to preoperative fluid deprivation, or to a reduction in cardiac output and thus liver blood flow as a result of anaesthesia [2].

The fact that the relative proportions of the four metabolites were similar to those measured in volunteers by radiochemical techniques demonstrates that NMR is a valid method for the quantification of metabolites of propofol.

REFERENCES

1. Simons PJ, Cockshott ID, Douglas EJ, Gordon EA, Hopkins K, Rowland M. *Xenobiotica* 1988; 18: 429–440.
2. Lange H, Stephan H, Riecke H, Kellerman M, Sonntag H, Bircher J. *British Journal of Anaesthesia* 1990; 64: 563–570.

REGURGITATION OF GASTRIC CONTENTS DURING GENERAL ANAESTHESIA USING THE LARYNGEAL MASK AIRWAY

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Aspiration of gastric contents associated with the use of laryngeal mask airways has been reported recently [1, 2]. We compared the incidence of regurgitation of gastric contents in spontaneously breathing patients under general anaesthesia administered via a face mask and Guedel airway or a laryngeal mask airway.

Thirty patients undergoing minor surgery were enrolled in the study. Patients who were obese or had a history of oesophageal reflux, hiatus hernia, or previous gastric surgery were excluded. Patients were allocated randomly to receive anaes-

TABLE XIII. Patient characteristics (mean (SD) [range]). LMA = Laryngeal mask airway; FMGA = face mask and Guedel airway

	LMA group	FMGA group
n	15	15
Sex (M:F)	9:6	10:5
Age (yr)	49.1 [23–69]	47.7 [24–70]
Weight (kg)	68.4 (2.5)	68.2 (1.9)
Surgery (min)	31.6 (2.1)	29.3 (2.2)

thetic gases via either a laryngeal mask airway (group LMA) or a face mask and Guedel airway (group FMGA). All patients were premedicated with temazepam 10–20 mg. Anaesthesia was induced with propofol 2 mg kg⁻¹ and fentanyl 1 µg kg⁻¹, and maintained with halothane and nitrous oxide in 33% oxygen via a Magill circuit. Airways were inserted shortly after induction of anaesthesia by anaesthetists experienced in the technique.

Ten minutes before induction of anaesthesia, a gelatin capsule containing 25% methylene blue in lactose was given to all patients with water 20 ml in the sitting position. At the end of the surgical procedure and before termination of anaesthesia, the larynx and pharynx were inspected by laryngoscopy. Presence of blue dye was taken to represent regurgitation of gastric contents. Data were analysed using Student's *t* test and chi-square test.

The groups were comparable for sex, age, weight and duration of surgery (table XIII). Five patients (33%) in the LMA group regurgitated. No regurgitation was detected in the FMGA group (*P* < 0.05).

These data suggest that the incidence of regurgitation of gastric contents may be increased during general anaesthesia with spontaneous ventilation using the laryngeal mask airway.

REFERENCES

1. Wilkinson PA. *Anaesthesia* 1990; 45: 167.
2. Cyana AM, MacLeod DM. *Anaesthesia* 1990; 45: 167.

INVESTIGATION OF THE EFFECT OF ORAL DIAZEPAM ON UPPER AIRWAY REACTIVITY

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Assessment of upper airway reactivity using small inspired concentrations of ammonia has been described [1]. A threshold response to ammonia (NH₃TR) is defined as the smallest inspired concentration of ammonia which produces a sudden closure of the vocal cords (glottic stop) or a cough. Using this technique, Groves, Rees and Rosen [2] demonstrated a 200% increase in NH₃TR which persisted for 4 h after injection in subjects administered diazepam 15 mg i.v. Using a new, modified system for assessing ammonia thresholds we investigated the effect of a premedicant dose of oral diazepam.

Six non-smoking, healthy, male volunteers aged 25–35 yr were entered in a double-blind crossover study. Subjects abstained from alcohol from 12:00 the previous day and had

TABLE XIV. Mean change (%) from baseline of threshold response to ammonia (NH_3TR) and reaction time to an auditory stimulus (ART) in the diazepam and placebo groups

Time (min)	Placebo group		Diazepam group	
	ART	NH_3TR	ART	NH_3TR
30	-2.2	+25.0	+9.4	+58.8
60	-3.5	-6.6	+14.4	+155.5
90	+0.6	-1.7	+29.6	+92.6
120	+2.0	+5.8	+30.4	+157.2
150	-1.2	+10.8	+9.8	+80.5
180	-1.1	-14.2	+4.7	+55.4
210	+6.1	-7.5	+5.0	-12.9
240	+3.4	+12.5	+0.4	+6.7

a light breakfast on the day of study. Baseline NH_3TR and reaction time to an auditory stimulus (ART) were measured. The subjects were then given either diazepam 20 mg orally or placebo on separate occasions at least 1 week apart. Measurements of ART and NH_3TR were made every 30 min for the next 4 h. NH_3TR was measured in order of increasing concentration of ammonia, stopping at one level above that at which a clear glottic stop or cough had been obtained.

Mean percentage changes from baseline of NH_3TR and ART for the six subjects are shown in table XIV.

It would appear from these initial results that a pre-medicant dose of oral diazepam may increase NH_3TR and thus reduce upper airway reactivity, but by 4 h NH_3TR had returned to almost baseline values.

REFERENCES

1. Pontoppidan H, Beecher HK. *Anesthesiology* 1971; 35: 634-637.
2. Groves ND, Rees JL, Rosen M. *Anaesthesia* 1987; 42: 808-814.

COMPARISON OF THE EFFECTS OF PROPOFOL, MIDAZOLAM AND THIOPENTONE ON NEUTROPHIL POLARIZATION *IN VITRO*

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Anaesthetic agents have inhibitory effects on the immune system [1], although they are generally short-lived and reversible. However, these effects may be more important when the agents are administered continuously, in the intensive care unit (ICU), to patients whose immune system may be compromised already.

We compared the effect of propofol, midazolam and thiopentone on neutrophil polarization *in vitro*. Polarization is the initial response of neutrophils to a chemotactic stimulus and causes orientation in the direction of the stimulus. Propofol and midazolam are used frequently to produce sedation in ICU. Thiopentone, which is known to inhibit immune function [2], was included for comparison. Propofol is solubilized in a substance similar to 10% Intralipid which also affects

white cell function [3]. Therefore, the effect of 10% Intralipid alone was examined also.

Peripheral blood from healthy volunteers was sedimented with Dextran and the buffy coat centrifuged on Lymphoprep to obtain a neutrophil-rich cell pellet. Optimum neutrophil polarization was induced by incubating cells with 10^{-8} mol litre $^{-1}$ N-formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP) in the presence or absence of varying concentrations of each agent.

Propofol and thiopentone inhibited neutrophil polarization over a range of concentrations. Inhibition was approximately 100% at 10 times the plasma concentration required to produce anaesthesia. At plasma concentrations required for anaesthesia (propofol 6 $\mu\text{g ml}^{-1}$, thiopentone 40 $\mu\text{g ml}^{-1}$) inhibition was mean 49 (SD 5)% and 46 (3)%, respectively. At plasma concentrations of propofol required for sedation (3 $\mu\text{g ml}^{-1}$) inhibition was 47 (5)%. Midazolam produced minimal inhibition (0.1 (1.5)%) at plasma concentrations required for sedation (1.2 $\mu\text{g ml}^{-1}$); inhibition increased at 10 times this concentration but this was less than propofol or thiopentone. Intralipid produced augmentation of polarization at all concentrations. At a concentration used to carry 6 μg of propofol (i.e. 0.6 $\mu\text{l ml}^{-1}$) augmentation was 41 (7)%.

In conclusion, propofol and thiopentone inhibit neutrophil polarization to a similar degree *in vitro* at plasma concentrations required for anaesthesia. At plasma concentrations required for sedation, propofol produced more inhibition than midazolam.

REFERENCES

1. Moudgil GC. *Canadian Anaesthetic Society Journal* 1986; 33: S54-S60.
2. Salo M. *British Journal of Anaesthesia* 1989; 63: 716-720.
3. Fraser I, Neoptolemos J, Woods P, Bowry V, Bell PRF. *Clinical Nutrition* 1983; 2: 37-40.

CAN GLYCOPYRROLATE ATTENUATE PROPOFOL-INDUCED HYPOTENSION IN ELDERLY PATIENTS?

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Pretreatment with glycopyrrolate 5 $\mu\text{g kg}^{-1}$ has been proposed as a means of attenuating the hypotension induced by induction and maintenance of anaesthesia with propofol and alfentanil [1], although a larger study (which used propofol and fentanyl) failed to confirm this finding [2]. Elderly patients are particularly intolerant of hypotension and are especially likely to benefit from strategies which reduce hypotension associated with anaesthesia.

Twenty unpremedicated patients aged 65 yr or more undergoing elective urological surgery were allocated randomly to receive saline (group I, $n = 10$) or glycopyrrolate 5 $\mu\text{g kg}^{-1}$ (group II, $n = 10$), 5 min before anaesthesia in a double-blind study. Induction with propofol 100 mg min^{-1} until cessation of counting was followed by a maintenance dose of 10 $\text{mg kg}^{-1} \text{h}^{-1}$. Heart rate and arterial pressure (measured non-invasively) were recorded before induction and for 5 min afterwards. Patient characteristics and haemodynamic data are shown in table XV.

There were no significant between-group differences in

TABLE XV. Mean (SEM) patient characteristics and measurements of heart rate (HR) and mean arterial pressure (MAP). Pretreatment with saline (group I) or glycopyrrolate (group II) was given 5 min before induction

	Group I	Group II
Age (yr)	76.3 (1.8)	77.9 (2)
Sex (M:F)	6:4	8:2
Weight (kg)	66.6 (3.7)	59.6 (3.7)
ASA grade (I:II:III)	0:8:2	0:8:2
Induction dose of propofol (mg kg ⁻¹)	1.65 (0.07)	1.8 (0.01)
MAP (mm Hg)		
Baseline	118 (4.8)	112 (5.8)
1 min after pretreatment	121 (5.6)	116 (5.5)
4 min after pretreatment	116 (5.6)	114 (6.8)
2 min after induction	88 (6.1)	83 (5.4)
5 min after induction	91 (6.6)	88 (6.5)
HR (beat min ⁻¹)		
Baseline	75 (3.9)	71 (3.4)
1 min after pretreatment	76 (3.3)	77 (4)
4 min after pretreatment	74 (4.6)	82 (4.4)
2 min after induction	73 (3.4)	84 (5.3)
5 min after induction	71 (2.4)	80 (4)

either patient characteristics or mean arterial pressures. Heart rate was significantly increased by glycopyrrolate ($P < 0.001$, Mann-Whitney U test and analysis of variance).

We conclude that pretreatment with glycopyrrolate does not attenuate the hypotensive effect of propofol in elderly patients. A more useful clinical strategy may be reduced injection rate [3].

REFERENCES

1. Skues MA, Richards MJ, Jarvis AP, Prys-Roberts C. *Anesthesia and Analgesia* 1989; **69**: 386-390.
2. Sneyd JR, Berry A. *Anesthesia and Analgesia* 1991; **72**: S262.
3. Peacock JE, Lewis RP, Hunter S, Reilly CS. *British Journal of Anaesthesia* 1990; **64**: 391P-392P.

CORRESPONDENCE

SPINAL ANAESTHESIA IN OBSTETRICS

Sir,—In his review of spinal anaesthesia in obstetrics [1], Dr Kestin kindly attributed to me the first report of the combined spinal-extradural technique for Caesarean section. I have now performed well over 1000 sections using this approach and, for the reasons outlined by Dr Kestin, I believe that it provides consistently better anaesthesia and more flexibility than each technique used alone. Since first using the combined approach 15 years ago, for example, I have not yet found it necessary to resort to general anaesthesia.

Dr Kestin also referred to the absence of spinal headache that was reported in my previous communication [2]. Despite routine daily follow up until discharge from hospital, no patient has yet developed a dural puncture headache following this combined anaesthetic. I can assure you that no-one has been more surprised about this than I! Even using a 26-gauge needle, I would have anticipated a spinal headache to have occurred by now. The only explanation I can offer is that by using the extradural catheter for postoperative analgesia (pethidine 50 mg in saline 10 ml given on a patient-demand basis for up to 48 h after surgery) we are unwittingly providing prophylaxis against the development of spinal headache.

As Dr Kestin (and also Dr Carrie in another recent review [3]) has stated, a combined "needle-through-needle" technique seems to have become more popular than using two separate interspaces. The former approach obviously appears more attractive because the patient requires only one injection. I am concerned, however, that damage to the spinal needle tip might occur during its passage through the extradural needle and that this, combined with a directional change of the needle just before entering the dura, could traumatize the dura—and so increase the likelihood of spinal headache. I am even more concerned about any delay which might occur because of difficulty in threading the extradural catheter. In my view, after the spinal anaesthetic has been administered, the patient demands undivided attention and reassurance. For instance, the onset of spinal anaesthesia often leads to patient anxiety, and symptoms associated with hypotension need to be recognized and treated without delay. One should not be distracted by attempting to thread an extradural catheter. For these reasons, I still prefer to have the extradural catheter in place before proceeding to administer the spinal anaesthetic at a separate interspace.

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REFERENCES

1. Kestin IG. Spinal anaesthesia in obstetrics. *British Journal of Anaesthesia* 1991; 66: 596-607.
2. Brownridge P. Epidural and subarachnoid analgesia for Caesarian section. *Anaesthesia* 1981; 36: 70.
3. Carrie LES. Extradural spinal or combined block for obstetric surgical anaesthesia. *British Journal of Anaesthesia* 1990; 65: 225-233.

Sir,—Thank you for the opportunity to reply to Dr Brownridge. Although combined spinal-extradural techniques have become popular, there are few prospective studies of this technique. Much of the knowledge comes from anecdotal reports.

If Dr Brownridge has performed more than 1000 Caesarean sections using the combined technique without any postspinal headaches, then the upper 95% confidence limit for the true incidence of spinal headache is less than 0.3% [1]. This is much less than expected after using a 26-gauge needle in this population. This finding warrants further investigation by prospective controlled trials.

Dr Brownridge mentions two problems of the "needle-through-needle" method of the combined spinal-extradural technique. How much of a real risk there is of damaging the tip of the spinal needle as it traverses the side of the Tuohy needle is unknown, but it seems unlikely. There are Tuohy needles with an end-hole for the spinal needle and the side hole for the extradural catheter (Sterima SA, Zonnekestraat 13, 8620 Kortrijk, Belgium).

Difficulty threading the extradural catheter after the spinal injection has been given is a concern. For this reason, I think combined techniques using a "needle-through-needle" method should be performed only with the patient lying on her side. It may be alarming for the patient to develop a unilateral block, but she should be protected from developing severe hypotension by lying in the full lateral position. There are potentially much greater hazards in this event if the technique is being performed with the patient sitting upright.

If the extradural catheter is inserted first and a spinal injection performed at a different interspace, as suggested by Dr Brownridge, then there is a theoretical possibility of damaging the extradural catheter with the spinal needle. The magnitude of this risk is unknown.

I. G. KESTIN
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REFERENCE

1. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything alright? Interpreting zero numerators. *Journal of the American Medical Association* 1983; 249: 1743-1745.

FRESH GAS REQUIREMENT OF THE BAIN SYSTEM

Sir,—Dr Miller's article on rebreathing with various anaesthetic systems described an ingenious lung model for calculating the degree of rebreathing of alveolar gas into the alveolar compartment [1]. An important result from this study, which appears to have been overlooked, is that rebreathing with the Bain system was prevented by a fresh gas flow less than twice the minute volume ($\dot{V}_E$). This agrees with earlier work by Meakin and Coates in anaesthetized children [2], but is contrary to a previous assertion by Miller that at least $2\dot{V}_E$ is necessary for adults and $3\dot{V}_E$ for children [3].

G. MEAKIN
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REFERENCES

1. Miller DM. Early detection of "rebreathing" in afferent and efferent reservoir breathing systems using capnography. *British Journal of Anaesthesia* 1990; 64: 251-255.
2. Meakin G, Coates AL. An evaluation of rebreathing with the Bain system during anaesthesia with spontaneous ventilation. *British Journal of Anaesthesia* 1983; 55: 487-496.
3. Miller DM. Breathing systems for use in anaesthesia. Evaluation using a physical lung model and classification. *British Journal of Anaesthesia* 1988; 60: 555-564.

Sir,—Dr Meakin's astute observations that rebreathing in the Bain system, detected by capnography, at a level less than two times the minute ventilation ($2\dot{V}_E$) [1] could be claimed as rebreathing with a magnitude which may be of clinical importance. The actual curves, using the more sensitive and accurate method to discern rebreathing, showed that deviation from the maximum effective alveolar ventilation ($\dot{V}_{Ae}/\dot{V}_E$) line began at $2\dot{V}_E$. Why, then, should I have said in another earlier report that the recommended fresh gas flow ($\dot{V}_F$) for children should be $3\dot{V}_E$ [2]? This recommendation is based upon the difference in the magnitude of variability of metabolic rate between children and adults.

In the Magill or any other afferent reservoir system, the recommended $\dot{V}_F$ is equal to $\dot{V}_E$ and is greater than the point at which onset of rebreathing occurs (approximately 0.6-0.7 of the $\dot{V}_E$ [1, 2]). This is to allow for changes in carbon dioxide production ($\dot{V}_{CO_2}$) during anaesthesia. In the Bain system, the recommended $\dot{V}_F$ should be greater than this point, which may become clinically significant only when $\dot{V}_F$ is less than $2\dot{V}_E$. In children, the potential changes in $\dot{V}_{CO_2}$ are greater than in adults and it is therefore for practical reasons that I made the recommendation that $\dot{V}_F$ should be $3\dot{V}_E$ for all efferent reservoir or T systems. If one were monitoring the resting minute ventilation in children (and not many of us do), then I must agree that $\dot{V}_F$ equal to $2\dot{V}_E$ would indeed be acceptable.

D. MILLER
Tygerberg

REFERENCES

1. Miller DM. Early detection of "rebreathing" in afferent and efferent reservoir breathing system using capnography. *British Journal of Anaesthesia* 1990; 64: 251-255.
2. Miller DM. Breathing systems for use in anaesthesia. Evaluation using a physical lung model and classification. *British Journal of Anaesthesia* 1988; 60: 555-564.

PICOLAX BOWEL PREPARATION

Sir,—I was interested to read the abstract of the presentation to the Anaesthetic Research Society on the effects of Picolax on body weight and intravascular fluid [1]. The findings might account for the observation of Campbell and colleagues of the increased requirement for i.v. fluids during surgery for intestinal resection [2].

My experience in anaesthetizing patients for colon resection after Picolax bowel preparation is that these patients often need large volumes of i.v. fluids (up to 4 litre) to stabilize the arterial pressure after induction of anaesthesia. I have also heard anecdotal stories of collapse after bowel preparation with Picolax before radiological examination, and of one

patient who had a cardiac arrest. The manufacturers inform me that their packaging insert includes the instruction to encourage oral fluid intake when Picolax is used, but I found that many nurses were not aware of this, and that individual sachets of Picolax do not include this advice.

It is important that patients who are given Picolax are also given the instruction to drink quite large quantities of fluid. In a letter from the manufacturers, they describe a study in which patients drank 139 ml of water every 1 h for 12 h during treatment with Picolax, and serum sodium, potassium and osmolality results suggested that this produced only mild overhydration. If oral intake is impossible, fluids should be infused i.v.

M. E. DODSON
Liverpool

REFERENCES

1. Barker P, Trotter T, Hanning CD. Study of the effect of Picolax bowel preparation on body weight, cardiovascular variables and haemoglobin concentration. *British Journal of Anaesthesia* 1991; 66: 410P-411P.
2. Campbell IT, Baxter JN, Tweedie IE, Taylor GT, Keens SJ. I.v. fluids during surgery. *British Journal of Anaesthesia* 1990; 65: 726-729.

INTERFERENCE WITH PACEMAKER FUNCTION

Sir,—The recent case report by Dr Finfer [1], illustrates one of the inherent problems of a unipolar pacing system, that of inhibition by skeletal muscle myopotentials. Suxamethonium-induced muscle fasciculations were thought to be responsible for pacemaker failure. It has been suggested that a defasciculating dose of a non-depolarizing neuromuscular blocker should be used or suxamethonium avoided [2]. In addition, thiopentone has been documented to decrease pacemaker threshold [3], increasing the risk of ventricular arrhythmias [4].

Permanent pacemakers with bipolar electrodes are less sensitive to interference [5]. This has led to their increased use over recent years. During the 12-month period April 1990 to March 1991, 16 unipolar and 402 (96%) bipolar pacemakers were inserted at our hospital. Wider adoption of this practice will help reduce the problems encountered during anaesthesia.

V. S. SIDHU
London

REFERENCES

1. Finfer SR. Pacemaker failure on induction of anaesthesia. *British Journal of Anaesthesia* 1991; 66: 509-512.
2. Zaidan JR. Pacemakers. *Anesthesiology* 1984; 60: 319-334.
3. Siddons H, Sowton E. *Cardiac Pacemakers*. Springfield, Illinois: Thomas, 1967; 110, 113.
4. Scott DL. Cardiac pacemakers as an anaesthetic problem. *Anaesthesia* 1970; 25: 87-104.
5. Werner I. Interference in pacemakers. *Pace* 1984; 7: 1021-1048.

Sir,—Thank you for the opportunity to reply to this letter. The author quotes Zaidan in suggesting that a "defasciculating dose of non-depolarizing neuromuscular blocker should be used or suxamethonium avoided". Suxamethonium remains the neuromuscular blocker of choice for rapid sequence

induction of anaesthesia in patients at risk of aspiration of gastric contents; in such patients many anaesthetists would not wish to avoid its use.

Whilst it is possible that a defasciculating dose of non-depolarizing blocking drug may reduce the incidence of pacemaker inhibition by myopotentials, I am unaware of any published research that supports this suggestion. It is still my view that the safest way to avoid myopotential inhibition is to re-programme the pacemaker to asynchronous mode in those patients in whom the use of suxamethonium is indicated. There is no doubt that bipolar pacemakers are much less sensitive to myopotential inhibition and their widespread use would reduce the incidence of this problem. However, the majority of patients with pacemakers have unipolar systems *in situ* and it remains essential that anaesthetists ascertain the type of pacemaker before embarking on anaesthesia.

S. R. FINFER
Oxford

ANAESTHESIA AND BONE MARROW APLASIA

Sir,—I wish to comment on the case report by Fenner and Cashman [1]. To those of us who have a long standing interest in the toxicity of anaesthetic drugs and the habits developed in recommending specific anaesthetic agents, this article is of interest. Concerning the possible toxicity of agents involved, it is of interest that avoiding nitrous oxide did not avoid the neutropenia. I have even greater interest in the recommendation "to use anaesthetic techniques based on conduction block whenever possible in patients with this type of bone marrow aplasia". Conduction anaesthesia was not "tested" in this experience. The authors have therefore recommended something different without any supporting evidence—in the presence of the fact that the patient had three uneventful recoveries from the anaesthetics actually used.

W. K. HAMILTON
San Francisco

REFERENCE

1. Fenner SC, Cashman JN. Anaesthesia and congenital agranulocytosis: influence of anaesthetic agent on neutrophil numbers in a patient with Kostmann's syndrome. *British Journal of Anaesthesia* 1991; 66: 620-624.

Sir,—Thank you for the opportunity to reply to the letter from Dr Hamilton. We also were interested to note that the avoidance of nitrous oxide during the third anaesthetic did not prevent the occurrence of a further episode of profound neutropenia. It is possible that ketamine may have an effect on the bone marrow, but an effect caused by the neuroendocrine stress response, even from such a minor surgical procedure, cannot be excluded.

Dr Hamilton is correct to point out that we did not use a technique based on conduction block in any of the three anaesthetics given. However, we feel that such a technique is likely to provide the best possible chance for a beneficial outcome. Regional anaesthesia is associated with a decrease in the plasma concentrations of cortisol [1] and catecholamines [2] and a reduction in postoperative granulocytosis and leucopenia [1]. The changes in glucocorticoids and sympathetic amines are known to cause short-term depression of neutrophil migration and phagocytosis [3]. Local anaesthetic agents, and in particular bupivacaine, do not have marked

inhibitory effects on leucocytic phagocytosis except in large concentrations [4]. Although we have not provided the clinical evidence to support the use of conduction anaesthesia, in a case such as this we believe that there is sufficient evidence to substantiate such a recommendation.

S. G. FENNER
J. N. CASHMAN
London

REFERENCES

1. Rem J, Brandt MR, Kehlet H. Prevention of postoperative lymphopenia and granulocytosis by epidural analgesia. *Lancet* 1980; 1: 283-285.
2. Edwards AE, Smith CJ, Gower DE, Williams CP, Ferguson BJM, Gough J, Gemmell LW. Anaesthesia, trauma, stress and leucocyte migration: influence of general anaesthesia and surgery. *European Journal of Anaesthesiology* 1990; 7: 185-196.
3. Boxer LA, Stossel TP. Qualitative abnormalities of neutrophils. In: Williams WJ, Beutler E, Erslev AJ, Lichtman MA, eds. *Haematology*, 3rd Edn. New York: McGraw Hill, 1983; 802-815.
4. Moudgil GC. Effect of premedicants, intravenous anaesthetic agents and local anaesthetics on phagocytosis *in vitro*. *Canadian Anaesthetic Society Journal* 1981; 28: 597-601.

BACTERIAL GROWTH IN PROPOFOL

Sir,—Propofol infusions recently have been implicated as a medium supporting the growth of micro-organisms [1] and as a source of infection in patients following clean surgical procedures [2]. A study was performed to determine if contamination was extrinsic (contaminated during handling) or intrinsic (contaminated at the time of manufacture).

Under sterile conditions, two 60-ml syringes (A and B) were prepared with propofol, attached to 1.5-m length of PVC catheter and placed on a sterile surface. At 45-min intervals over a period of 6 h, 6 ml of propofol was withdrawn from each syringe. Three millilitre was injected into an aerobic blood culture bottle and 3 ml into an anaerobic blood culture bottle. These were incubated and examined at 24, 48, 96 and 168 h. No organisms were grown from either syringe.

The same procedure was repeated, but involved only washing of hands and placing the propofol on a clear surface; again two 60-ml syringes (C and D) were utilized and aerobic and anaerobic blood culture bottles inoculated every 45 min for 6 h. On this occasion *Staphylococcus aureus* and *S. epidermidis* were identified in an aerobic blood culture bottle after 48 h. This corresponded to sampling in syringe C after 90 min. A diphtheroid organism was identified in an aerobic blood culture bottle after 168 h. This corresponded to a sample from syringe D after 180 min. The propofol syringes were left for 24 h and the remaining propofol inoculated in two blood culture bottles. Culture was negative. A nasal swab from the author grew *S. aureus*.

Thus organisms were not cultured from propofol syringes after preparation using a sterile technique. However, three bacterial strains were isolated using a preparation technique similar to that used in clinical practice. Thus contamination was "extrinsic".

Recent surveys of anaesthetists show that aseptic technique and infection control is frequently not observed during anaesthesia [3]. Infection related to propofol infusions has

been associated with use of the same syringes in more than one patient [4]. This suggests that potentially severe infection can occur in patients on propofol infusions because of lack of aseptic technique.

The authors would recommend preparation of propofol infusions under aseptic conditions, the use of separate syringes and catheters for each patient and their replacement when the infusion requires changing.

G. A. McLEOD
N. PACE
M. D. INGLIS
Airdrie

REFERENCES

1. Thomas DV. Propofol supports bacterial growth. *British Journal of Anaesthesia* 1991; 66: 274.
2. Post-surgical infections associated with an extrinsically contaminated intravenous anaesthetic agent. California, Illinois, Maine and Michigan, 1990. *Morbidity and Mortality Weekly Report* 1990; 39: 426-433.
3. Rosenberg AD, Bernstein RL, Ramanathan S, Albert DB, Marshall MH. Do anesthesiologists practice proper infection control precautions? *Anesthesiology* 1989; 71: A949.
4. Kemper PM, Learned DW. Anesthesia practice: a vector of infection? *Anesthesiology* 1989; 71: A948.

SPEED OF ONSET OF ANALGESIA OF DIAMORPHINE OR MORPHINE

Sir,—We were interested by the report that morphine has a more rapid onset of action than diamorphine [1]. The accepted wisdom is that diamorphine, being more lipophilic than morphine, acts more quickly. That the converse is true implies that our understanding of the lipid solubility of drugs and the dynamics of their transport across membranes is incomplete.

Morphine-6-glucuronide (M6G), an active metabolite of morphine, has been shown to have a greater analgesic activity than would be expected from a compound considered to be highly polar and unable to cross the blood-brain barrier [2]. It has been shown now that M6G has a lipophilicity similar to that of morphine, and much greater than expected [3]. Force field and quantum mechanical calculations indicate that M6G can exist in two conformational forms. The extended form exposes the polar groups of the molecule to the solvent and thus the form is hydrophilic. In the other form, the molecule is folded so that its polar groups are inaccessible and the molecule is lipophilic. An equilibrium exists between the two forms such that the extended hydrophilic form predominates in polar media such as water, and the folded lipophilic form predominates in non-polar media, such as biological membranes. Morphine-6-glucuronide is able, therefore, to cross the blood-brain barrier more efficiently than expected and this may explain its clinically observed analgesic effect.

Diamorphine is metabolized to morphine through 6-acetyl morphine (6AM). This metabolite is able also to cross biological membranes more readily than would be expected by its apparently polar nature. Unlike M6G, 6AM does not appear to have conformational isomers. However, the 6AM molecule is shaped so that the OH groups of the morphine moiety are effectively masked and the molecule is rendered more lipophilic.

Conventional pharmacokinetic theory answers many questions and new investigative techniques are explaining some unresolved clinical anomalies. Our understanding of the behaviour of drugs in the body is incomplete and we should not be surprised, therefore, at such findings as morphine acting more rapidly than diamorphine.

M. P. SHELLY
Manchester
G. R. PARK
Cambridge

REFERENCES

1. Morrison LM, Payne M, Drummond GB. Comparison of speed of onset of analgesic effect of diamorphine and morphine. *British Journal of Anaesthesia* 1991; 66: 656-659.
2. Hanna MH, Peat SJ, Knibb AA, Fung C. Disposition of morphine-6-glucuronide and morphine in healthy volunteers. *British Journal of Anaesthesia* 1991; 66: 103-107.
3. Carrupt P-A, Testa B, Bechalany A, El Tayer N, Descas P, Perrissoud D. Morphine 6-glucuronide and morphine 3-glucuronide as molecular chameleons with unexpected lipophilicity. *Journal of Medical Chemistry* 1991; 34: 1272-1275.

FIRST USE OF COMBINED SPINAL-EXTRADURAL ANAESTHESIA

Sir,—In the interesting review of extradural, spinal or combined blocks for obstetric surgical anaesthesia [1], Brownridge is described as the inventor of the combined spinal-extradural technique. However, Brownridge suggested it in February 1979 [2], but described its use in Caesarean section only in 1981 [3].

I had cited him as the first user of this method while describing our combined spinal-extradural needle [4]. However, Curelaru, and not Brownridge, was the first to use this technique [5], and described it in February 1979. He tested the method in 150 patients, using two vertebral punctures for the procedure, and described its advantages as the possibility of obtaining high quality conduction anaesthesia, minimal toxicity, absence of postoperative pulmonary complications and economy.

Twelve years have elapsed since that publication, which should be cited in further publications of the method.

J. ELDOR
Jerusalem

REFERENCES

1. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *British Journal of Anaesthesia* 1990; 65: 225-233.
2. Brownridge P. Central neural blockade and Caesarean section, Part 1. Review and case series. *Anaesthesia and Intensive Care* 1979; 7: 33-41.
3. Brownridge P. Epidural and subarachnoid analgesia for elective Caesarean section. *Anaesthesia* 1981; 36: 70.
4. Eldor J, Chaimsky G. Combined spinal-epidural needle (CSEN). *Canadian Journal of Anaesthesia* 1988; 35: 537-539.
5. Curelaru I. Long duration subarachnoid anaesthesia with continuous epidural block. *Praktische Anästhesie Wiederbelebung und Intensivtherapie* 1979; 14: 71-78.

Sir,—Thank you for the opportunity to comment on Professor Eldor's letter. I should now agree with him that Curelaru [1] in 1979 was the first to publish a description of a combined spinal and extradural (CSE) technique which involved the insertion of the spinal and extradural needles at separate lumbar interspaces.

My article [2] was submitted for publication in February 1990 and it was not until later that year that I (and also, I understand, Professor Eldor) learned from a most interesting exchange of letters with Professor Curelaru, of the latter's publication of his description in 1979. Professor Curelaru worked on the technique while an anaesthetist in Romania, where the poor standard of equipment available at the time for both general and regional anaesthesia led to his search for a more effective and reliable technique.

While the origin of many innovations seems to lead back inevitably to Biblical times, the first description of any type of CSE technique which I can find dates only from 1937! In that year, Soresi [3] described an "episubdural technique", which comprised an extradural injection with a single needle which was then advanced through the dura mater into the subarachnoid space to perform a spinal block. The author made the unlikely claim of a duration of action of 24–48 h even with the short-acting procaine. The technique was often preceded by the author's (a surgeon, not an anaesthetist) favourite premedication of "wine proctoclysis" which now would certainly be considered to be the misplaced use of 100–250 ml of port wine—*per rectum*! The method (but not the premedication) was revived recently by Sprötte and colleagues using their atraumatic needle [4]. However, the technique required the patient to be left rather awkwardly with the needle *in situ* until the extent and efficacy of the extradural block had been assessed. The needle was pushed through the dura mater to perform additional spinal anaesthesia only if the extradural block was inadequate.

To the best of my knowledge, credit for the first CSE technique by a single interspace spinal needle *through*

extradural needle technique should go to Coates [5], who passed a 26-gauge spinal needle through a 16-gauge extradural needle in orthopaedic patients. Muntaz, Daz and Kuz [6] also described a needle-through-needle technique in the same journal (indeed on the same page) as the Coates letter. Another variation is to use a single vertebral interspace, but to pass the spinal alongside the extradural needle in some type of guide, after the extradural space has been identified and a catheter introduced. Professor Eldor himself was the first to describe a device of this type [7].

I shall be neither surprised nor disappointed if publication of this letter leads to further revelations concerning the origin of the combined spinal-extradural technique.

L. E. S. CARRIE
Oxford

REFERENCES

1. Curelaru I. Long duration subarachnoid anaesthesia with continuous epidural block. *Praktische Anästhesie Wiederbelebung und Intensivtherapie* 1979; 14: 71–78.
2. Carrie LES. Extradural spinal or combined block for obstetric surgical anaesthesia. *British Journal of Anaesthesia* 1990; 65: 225–233.
3. Soresi AL. Episubdural anesthesia. *Anesthesia and Analgesia* 1937; 16: 306–310.
4. Sprötte G, Schedel R, Pajunk H, Pajunk H. Eine "atraumatische" Universalkanüle für einzeitige Regionalanästhesien. *Regional-Anaesthesie* 1987; 10: 104–108.
5. Coates MB. Combined subarachnoid and epidural techniques. *Anaesthesia* 1982; 37: 89–90.
6. Muntaz MH, Daz M, Kuz M. Another single space technique for orthopaedic surgery. *Anaesthesia* 1982; 37: 90.
7. Eldor J, Chaimsky, G. Combined spinal-epidural needle (CSEN). *Canadian Journal of Anaesthesia* 1988; 35: 537–539.

BOOK REVIEWS

Regional Anaesthesia, 2nd Edn. Edited by W. Koester, M. Kreuscher, H. C. Niesel and M. Zenz. Published by Mosby Year Book, St Louis. Pp. 299; indexed; illustrated. Price £64.00.

This is the second edition of a translation of a German text produced in association with Astra, consisting of chapters by 25 German contributors. It is produced on good quality paper and its strength lies in the excellent quality of the photographs and drawings showing surface markings and anatomy.

The first three chapters comprise general topics on regional anaesthesia. These tend to be somewhat superficial and dogmatic and unsupported by textual references. Alternative texts exist which discuss this material in greater depth.

The main part of the book comprises chapters on regional techniques, allocated to sections on surgery, obstetrics and pain therapy. Curiously, both ilioinguinal block and intercostal block appear in the section devoted to chronic pain, although these techniques are used frequently perioperatively to provide postoperative analgesia. The chapters are somewhat repetitive in their advice with regard to assessment of the patient and equipment required.

The main impression given by these chapters is that they are somewhat unbalanced, with little discrimination between blocks which are used commonly and those less commonly used. Curious dogmatic and unreferenced statements abound. There are some surprising omissions: for example, there is no discussion of the use of fine spinal needles or combined extradural-subarachnoid block, no mention of spinal catheters and more importantly, inadequate discussion of the use of test doses for extradurals. There are also some curious inclusions, for example the use of a hanging drop in subarachnoid block and a chapter on paracervical block in obstetrics.

Whilst the book may be attractive to anaesthetists in training, because of its high quality diagrams and detailed explanations, candidates for examinations wishing a more in-depth analysis of regional anaesthesia would need to consult other texts in addition.

D. Fell

Ambulatory Anaesthesia and Sedation. Impairment and Recovery. Edited by I. D. Klepper, L. D. Sanders and M. Rosen. Published by Blackwell Scientific Publications, Oxford. Pp. 297; indexed; illustrated. Price £39.50.

This book arose as a result of a workshop held in Cardiff in July 1988 and was written by anaesthetists, psychologists and pharmacologists actively involved in research. There are 24 chapters divided into five sections. The first section establishes the context and criteria for assessing recovery from drugs and compares the effects with those seen after ingestion of alcohol. A particularly important chapter written by Christopher Heneghan (who is both an anaesthetist and a barrister) outlines the legal position of the anaesthetist who allows patients to go home on the day of surgery. He makes quite clear the need for anaesthetists to protect themselves against being sued for

negligence by recording the warning given to patients that they may still be under the influence of anaesthetic drugs which could be implicated in an accident.

The second section discusses methods of assessing impairment and includes autonomic and neuromuscular function. Other chapters concentrate on body sway, eye movements, vigilance, reaction time, memory function and subjective assessment. In general, the pitfalls of measurement are discussed well although, even to someone interested in the field, the topics make dry reading.

The third section covers the practical application of recovery assessment to specific patient groups, namely those going back to work, the elderly and children. The point is made that an occupational history should be taken and particularly, what is actually involved in the job. Thus the consequences of cognitive failure can be entered into the equation when advising return to work.

The fourth section looks at the effects of benzodiazepines, analgesic drugs, i.v. and inhalation anaesthetics. The final section addresses the problem of new drugs. Inevitably, there is some overlap of information.

Although the subject matter is important to anaesthetists, I am disappointed not to be able to recommend individuals or libraries to buy this book. The subjects are covered to greater depth than most individuals will wish to delve. Conversely, the researcher in the field will probably prefer to start with a review article and then refer to the original publications.

G. Cooper

Intraoperative Use of Echocardiography. (A Society of Cardiovascular Anesthesiologists Monograph.) Edited by N. P. deBruijn and F. M. Clements. Published (1991) by J.B. Lippincott Company, Philadelphia. Pp. 225; indexed; illustrated. Price \$49.95.

The editors have enlisted 16 colleagues, all acknowledged experts in the field of intraoperative echocardiography, to write the 10 chapters of this superb book. It starts with a brief review written by Clements on the evolution of a new specialty: that of "anesthesiologist-echocardiographer", spelling out the training requirements. This is followed by a technical chapter by Thys and Hillel explaining in detail how echocardiography works. Several terms we have all heard or read about are explained clearly, often with the help of excellent diagrams. Two chapters are devoted to the detection of myocardial ischaemia (Cahalan) and the assessment of left ventricular function (Leung, Shiller and Mangano). These chapters show both the value of echocardiography and its limitations. The chapter by Stanley introduces the concept of quantitative echocardiography, giving details of algorithms used to determine chamber volume from two-dimensional echocardiograms, and suggesting elegant ways in which regional function may be quantified. The basic principles of Doppler colour-flow imaging are described by Sheikh, Adams and Kisslo. Again, disadvantages and limitations are discussed with the help of a few (paradoxically) black and white diagrams. In

addition to detection of ischaemia and evaluation of acute changes in left ventricular function, transoesophageal echocardiography plays an important role in the assessment of valvular disorders and in the intraoperative assessment of the quality of surgical repair. This issue is addressed by deBruijn and Clements. A natural extension is to consider the place of echocardiography in the assessment of congenital heart disease: Greeley and Ungerleider present data showing the impact of echocardiography in terms of surgical outcome, stressing the point that echocardiography makes it possible to repair residual defects before termination of anaesthesia, thus reducing the extent of reoperation and substantially decreasing the risk of surgical death. This type of evaluation may rest on transoesophageal or on epicardial (sterile) intraoperative echocardiography. This theme is extended to the adult patient by Czer and Maurer in their chapter devoted to Doppler colour-flow mapping. This may prove invaluable in the assessment of regurgitant flow, outflow obstruction, and identification of site of septal defects after myocardial infarction. In the last chapter Abel and Nishimura describe the principles of pulsed-wave Doppler echocardiography and discuss its many applications, from the measurement of cardiac output, the calculation of pressure gradients across a valve, the determination of mitral valve area, to the assessment of diastolic function based on the analysis of the mitral flow velocity curve.

A wealth of information is presented with simplicity and clarity. This information is extremely useful, not only to those who might wish to become "anesthesiologist-echocardiographers" but, more importantly, to all anaesthetists who want to understand what echocardiography can offer, be better able to interpret the findings, and assess the material presented in the increasing number of articles in the anaesthetic literature relating echocardiographic studies. Time has come to take stock of echocardiography in anaesthetic practice. This book does justice to this important subject and both editors and all

the contributors deserved to be congratulated for the high quality of their contributions. A book that should find its way to departmental libraries and in the hands of those involved in cardiovascular anaesthesia.

P. Foëx

A Pocket Book of Intensive Care: Data, Drugs and Procedures, 2nd Edn. Edited by J. Tinker and S. N. Jones. Published by Edward Arnold, Sevenoaks. Pp. 166; indexed; illustrated. Price £9.95.

The second edition of this highly popular pocket book has expanded by only 16 pages and now consists of 166 pages. The format remains unchanged and it contains the same eight chapters as the original.

The Publishers' notes on the back cover claim that the chapters on the renal, nervous and respiratory systems have been revised extensively. Unfortunately, there are only minimal changes in the renal and nervous system chapters (I could detect only one for the nervous system) and the opportunity has been missed to include such up to date techniques as continuous arteriovenous haemodialysis.

The respiratory chapter includes a useful new section on artificial ventilation. There is, however, no mention of minitracheotomy in the techniques section, and the book continues to advocate the use of an "Argyle trocar" to pierce the tissues beyond the subcutaneous layer when inserting a chest drain—a practice which should surely be abandoned in the light of ATLS Teaching.

Despite these criticisms, the book contains much useful data, in a readily accessible form, and should justifiably remain a valuable and popular source of "handy" information to the resident in Intensive Care.

G. W. Jones

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

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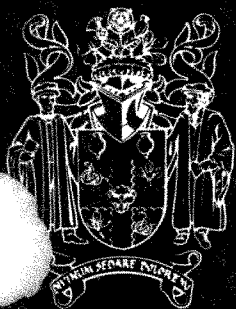
CONTENTS

	PAGE		PAGE
EDITORIALS: I. Resistance to non-depolarizing neuromuscular blocking agents	511	Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice	603
J. M. Hunter		D. G. Stott and B. J. Pleury	
II. Jaw stiffness—an ill understood condition	515	Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanose and strychnine	608
J. M. Saddler		W. M. Al-Muhandis, G. R. Lauretti and B. J. Pleury	
ORIGINAL ARTICLES		Determination of contamination of a chemical warfare-proof operating theatre with volatile anaesthetic agents and assessment of anaesthetic gas scavenging systems	614
Airway obstruction associated with the use of the Guedel airway	517	S. Yoganathan, I. G. Johnston, C. J. Parnell, I. T. Houghton and J. Restall	
A. M. Marsh, J. F. Nunn, S. J. Taylor and C. H. Charlesworth		RAPID COMMUNICATIONS	
Changes in amplitude and latency of the P300 component of the auditory evoked potential with sedative and anaesthetic concentrations of nitrous oxide	524	Haemodynamic effects of propofol: induction with 2.5 mg kg ⁻¹	618
J. Jessop, D. E. Griffiths, P. Furness, J. G. Jones, D. J. Sapsford and D. A. Breckon		J. E. Fairfield, A. Dritsas and R. J. Beale	
Effects of i.v. lignocaine on psychological performance and subjective state in healthy volunteers	532	Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block	621
P. J. Armstrong, L. M. Morrison, D. Noble, W. A. Sinclair, B. Tiplady and J. A. W. Wildsmith		K. K. Pihlajamäki	
Propofol and midazolam act synergistically in combination	539	CASE REPORTS	
T. G. Short and P. T. Chui		Resistance to atracurium in a patient with an increase in plasma alpha ₂ globulins	623
Intra-arterial thiopentone is directly toxic to vascular endothelium	546	A. J. Tatman, S. R. Wrigley and R. M. Jones	
R. D. MacPherson, L. J. McLeod and A. J. Grove		Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia	626
Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor	553	M. K. Reeder, A. D. Muir, P. Foëx, M. D. Goldman, L. Loh and D. Smart	
P. J. D. Andrews, N. M. Dearden and J. D. Miller		Unusual presentation of acute upper airway obstruction caused by an anterior mediastinal mass	632
Ketamine for caudal analgesia in children: comparison with caudal bupivacaine	559	T. M. Akhtar, S. Ridley and C. J. Best	
M. Naguib, A. M. Y. Sharif, M. Seraj, M. El Gammal and A. A. Dawlatly		Transient ischaemic attack after spinal anaesthesia ..	635
Maternal temperature regulation during extradural analgesia for labour	565	R. A. Chung and A. M. Goodwin	
W. R. Camann, L. A. Hortvet, N. Hughes, A. M. Bader and S. Datta		APPARATUS	
Clearance of atracurium and laudanose in the urine and by continuous venovenous haemofiltration ..	569	Temperature dependence of LED and its theoretical effect on pulse oximetry	638
E. S. Shearer, E. P. O'Sullivan and J. M. Hunter		K. J. Reynolds, J. P. de Kock, L. Tarassenko and J. T. B. Moyle	
Intraoperative assessment of atracurium-induced neuromuscular block using double burst stimulation	574	ABSTRACTS	
N. Braude, H. A. L. Vyvyan and M. J. Jordan		Proceedings of the Anaesthetic Research Society, Manchester Meeting, July 12-13, 1991	644P
Alcohol after sedation with i.v. midazolam-fentanyl: effects on psychomotor functioning	579	CORRESPONDENCE	
J. L. Lichtor, J. Zacny, J. L. Apfelbaum, B. S. Lane, G. Rupani, R. A. Thisted, C. Dohrn and K. Korttila		Spinal anaesthesia in obstetrics	663
Clinical and haemodynamic effects of milrinone in the treatment of low cardiac output after cardiac surgery	585	Fresh gas requirement of the Bain system	663
E. M. Wright and K. M. Sherry		Picolax bowel preparation	664
Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine	591	Interference with pacemaker function	664
R. Wenstone, J. M. Campbell, P. D. Booker and R. McKay		Anaesthesia and bone marrow aplasia	665
Influence of hypertonic volume replacement on the microcirculation in cardiac surgery	595	Bacterial growth in propofol	665
J. Boldt, B. Zickmann, C. Herold, M. Ballesteros, F. Dapper and G. Hempelmann		Speed of onset of analgesia of diamorphine or morphine	666
		First use of combined spinal-extradural anaesthesia	666
		BOOK REVIEWS	
		Regional Anaesthesia, 2nd Edn.	668
		Ambulatory Anaesthesia and Sedation, Impairment and Recovery	668
		Intraoperative Use of Echocardiography	668
		A Pocket Book of Intensive Care: Data, Drugs and procedures, 2nd Edn	669

VOLUME 67 • NUMBER 6 • DECEMBER 1991

145

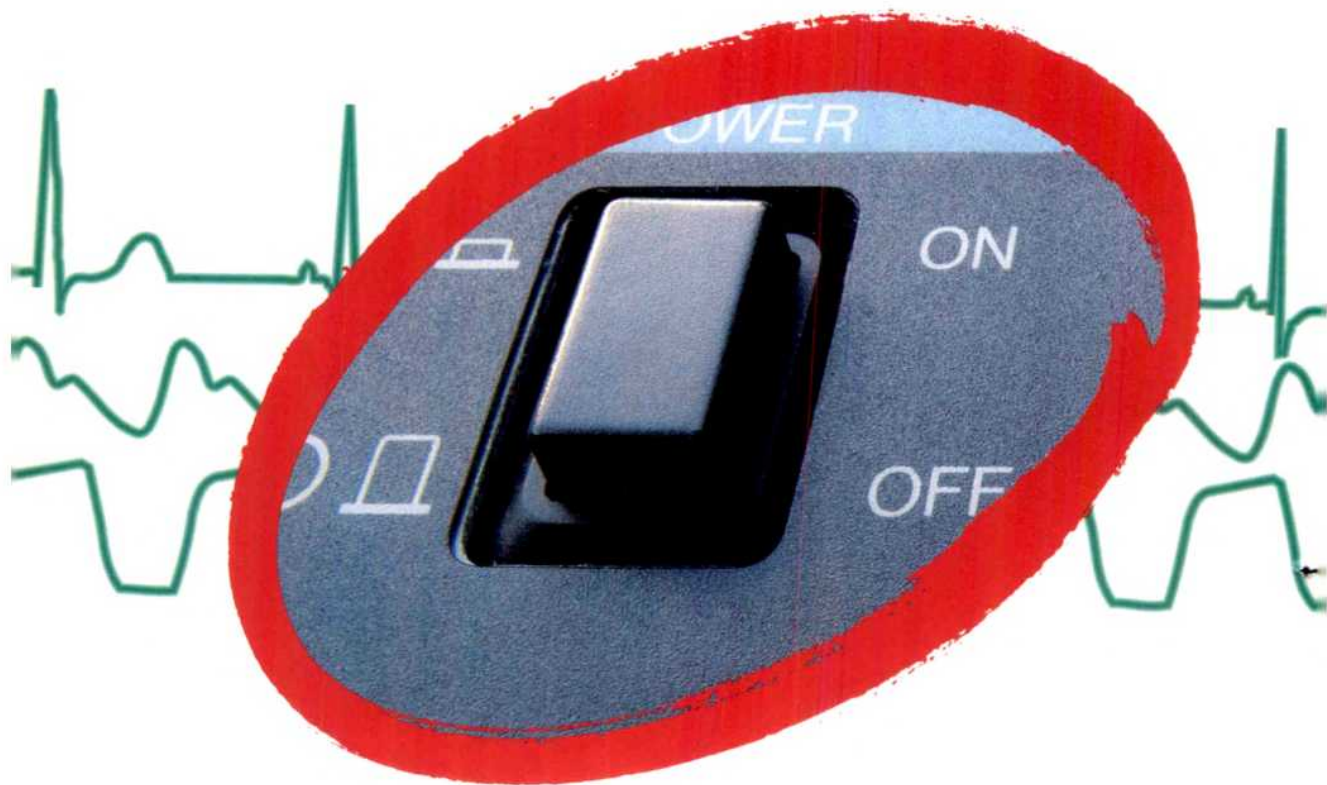
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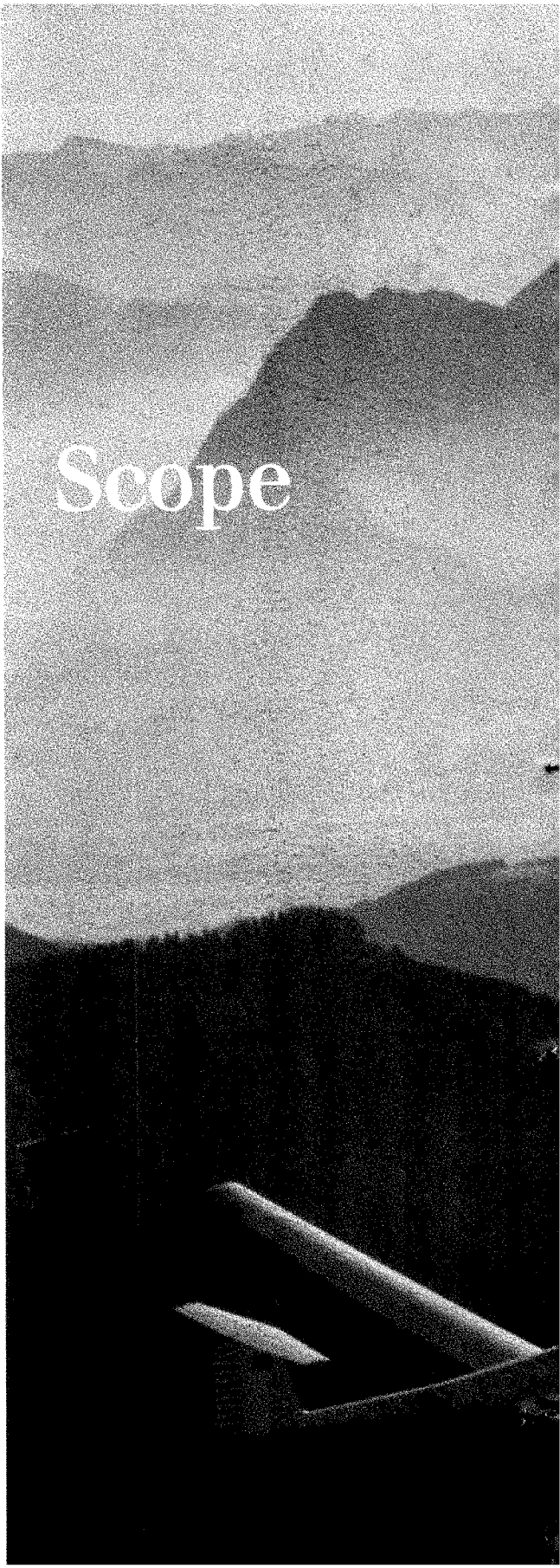
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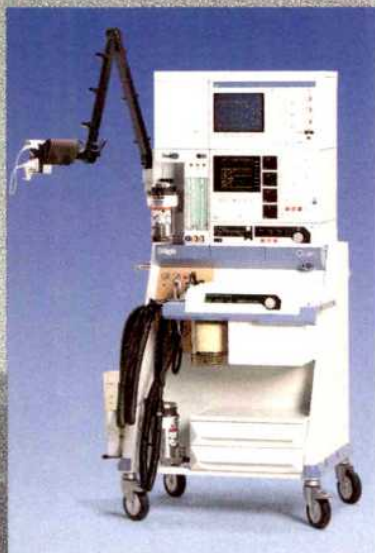
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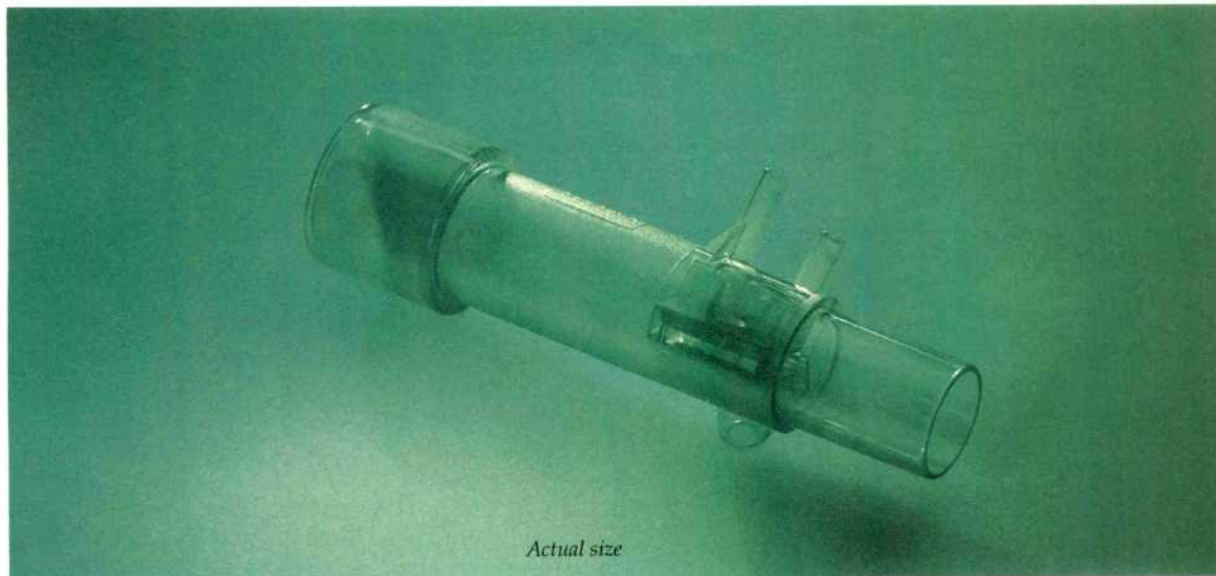
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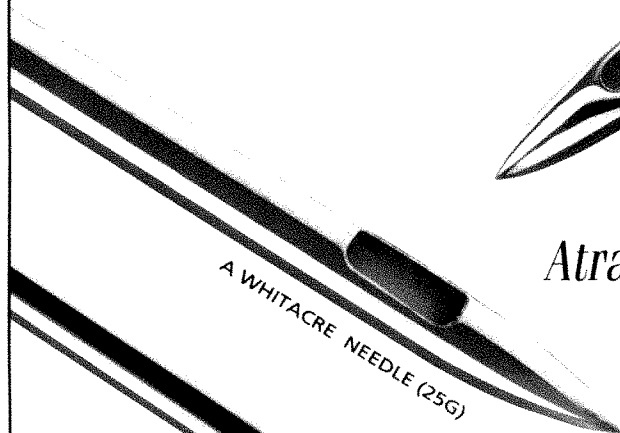
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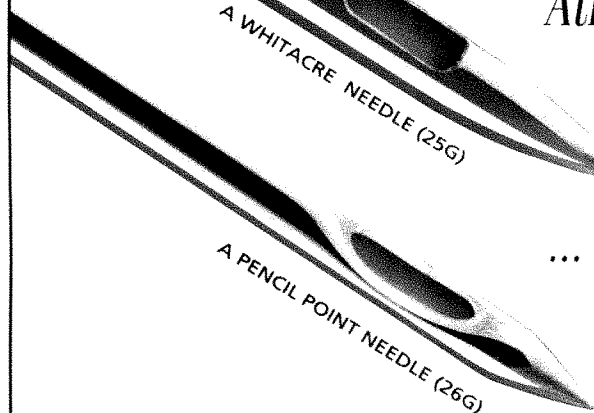
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Anästhesiologische Probleme beim
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Originalien
P. Saur, D. Kettler, H. Sonntag
Hämodynamische Parameter zur Abschätzung
des myokardialen Sauerstoffverbrauchs in der
Anästhesie
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W. Furtwängler, Th. J. Lugin
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peripheral circulation in
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Contents

Originalien

Hämodynamische Parameter zur Abschätzung des myokardialen Sauerstoffverbrauchs in der Anästhesie

P. Saur, D. Kettler und H. Sonntag

Zentrum Anaesthesiologie der Universität Göttingen

Hemodynamic variables reflecting myocardial
oxygen consumption in anaesthesia

Abstract. Direct measurements of myocardial oxygen consumption (MI_{O_2}) and of a number of hemodynamic variables were performed in 40 patients with coronary heart disease undergoing three vessel coronary artery bypass surgery. Anesthetic procedures included halothane, enflurane, isoflurane, propofol, fentanyl, midazolam, fentanyl, and morphine anesthesia. The following hemodynamic variables were correlated with MI_{O_2} : heart rate (HR), cardiac index (CI), stroke volume index (SVI) and anesthetic combined variables ($P_{aO_2} \times CI$, $P_{aO_2} \times HR$, $P_{aO_2} \times SVI$, $P_{aO_2} \times CI \times HR$, $P_{aO_2} \times CI \times SVI$, $P_{aO_2} \times CI \times HR \times SVI$). The product of $P_{aO_2} \times CI$ (HR) is equivalent to the tension time index as modified by Bretschneider and the index of Sarnoff as modified by Robinson. Production and uptake of lactate as metabolic equivalents of myocardial oxygen consumption were also correlated with myocardial oxygen consumption. Measurements were performed without surgical stimulation, during induction of anaesthesia, and after the operation. We obtained 209 evaluable measurements (MI_{O_2} vs hemodynamic variables). The single hemodynamic variables that correlated best with MI_{O_2} was stroke volume ($r = 0.71$) and heart rate ($r = 0.72$). Stroke volume index ($r = 0.71$) and heart rate ($r = 0.72$) were poorly correlated. The combined hemodynamic variables that correlated most closely with MI_{O_2} were the tension time index ($r = 0.71$) and the index of Sarnoff as modified by Robinson ($r = 0.72$). Production and consumption of lactate were not correlated with myocardial oxygen consumption. There was no difference in the correlation between MI_{O_2} and volatile as opposed to intravenous anaesthesia. These results indicate that MI_{O_2} cannot be estimated from stroke volume, blood pressure and heart rate alone. There are no safe limits for blood pressure, heart rate and rate pressure

product that exclude myocardial ischemia. Because of regional differences in the myocardial oxygen consumption, ischemia cannot be detected solely from arterial-lactate differences. It is not admissible to assume "safe limits" of hemodynamic variables. Rather, individual monitoring is mandatory during anaesthesia and operation. Adequate close monitoring of blood pressure, heart rate and ECG may help to detect myocardial ischemia.

Zusammenfassung. An 40 Patienten mit koronarer Herzkrankheit, die sich einer koronaren Bypass-Operation unterzogen, wurden direkte myokardiale Sauerstoffverbrauchsuntersuchungen und hämodynamische Messungen unter dem Einfluß folgender Anästhetika durchgeführt: Halothan, Enfluran, Isofluran, Propofol, Fentanyl, Midazolam, Fentanyl und Morphin. Folgende hämodynamische Parameter wurden mit dem myokardialen Sauerstoffverbrauch korreliert: maximale systolische (P_{aO_2}), Herzfrequenz (HR), Herzindex (CI) und Schlagvolumenindex (SVI). Aus den Einzelparametern wurden durch Multiplikation folgende Kombinationsparameter gebildet, die ebenfalls mit dem direkten myokardialen Sauerstoffverbrauch korreliert wurden: $P_{aO_2} \times CI$ (HR), $P_{aO_2} \times HR$, $P_{aO_2} \times SVI$, $P_{aO_2} \times CI \times HR$, $P_{aO_2} \times CI \times SVI$, $P_{aO_2} \times CI \times HR \times SVI$. Das Produkt $P_{aO_2} \times CI$ (HR) entspricht dem modifizierten Tension-Time-Index nach Bretschneider, das

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F	Volume. Large volumes...	(italics, indent)

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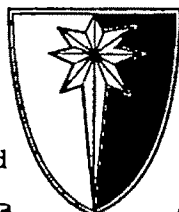
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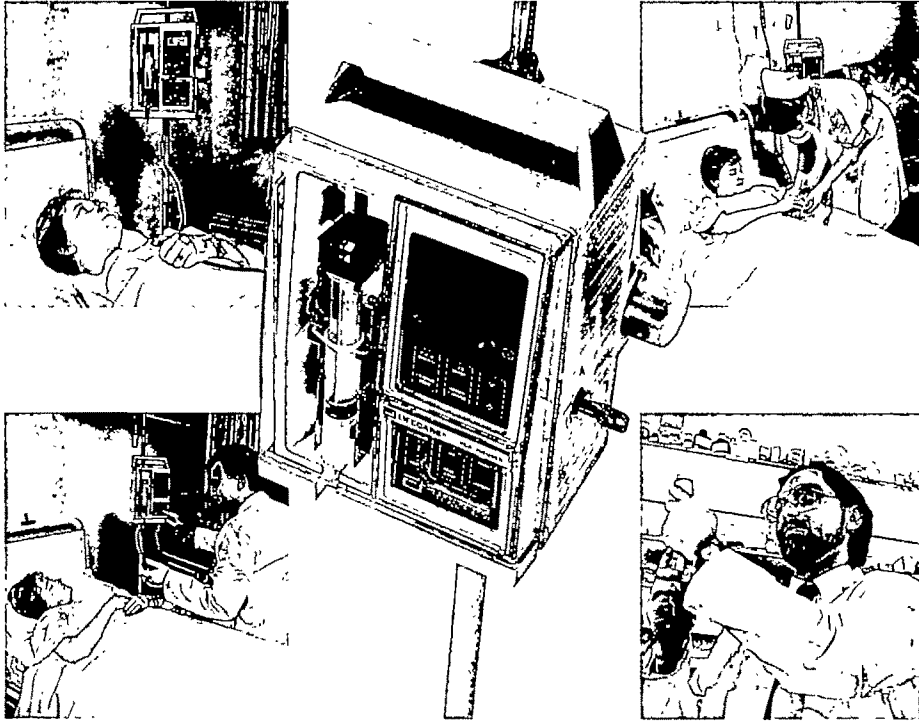
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EDITORIAL I

ASSESSMENT OF THE PLACENTAL CIRCULATION

The wellbeing of the fetus is dependent on the development and maintenance of an adequate fetal and uteroplacental circulation. At term, total uterine blood flow is 10% of the maternal cardiac output, of which 70–80% (about 600–700 ml min⁻¹) flows through the placenta [1]. The volume of all intervillous spaces has been estimated at 150–250 ml and there are approximately 60 placental cotyledons. The surface area of the mature placenta is about 11 m², so that the low flow to large surface area favours its use as a feto-maternal transfer organ [2].

The uterine vascular bed is dilated almost maximally under normal conditions, with little ability to dilate further [3]. It is not autoregulated, flow being dependent on perfusion pressure, which is related directly to the difference between uterine artery and venous pressures, and inversely to uterine vascular resistance. Changes in uterine arterial pressure without alteration in vascular resistance cause changes in placental blood flow. The hypotension associated with the supine position, regional or general anaesthesia or hypovolaemia results in decreased uteroplacental blood flow. Alpha-adrenergic stimulation vasoconstricts the uterine vascular input and, despite the increase in maternal arterial pressure, there is a reduction in placental perfusion [4].

On the fetal side of the placental circulation, the villi are supplied by two umbilical arteries. These thick-walled, highly contractile vessels have both alpha- and beta-adrenoreceptors which do not exist in the umbilical cord vessels [5]. The terminal villi contain an extensive sinusoidal network of small vessels which drain into a single thin-walled, distensible umbilical vein. Blood flow in the fetal placental circulation is about 250 ml min⁻¹. The umbilical placental circulation has a low resistance and changes of flow vary directly with changes in fetal cardiac output, which is dependent on stroke volume and heart

rate [6]. Biochemical factors may also play an important part in regulation of umbilical blood flow. The interdependence of the uteroplacental and fetoplacental circulations and the susceptibility to changes in maternal arterial and venous pressures may be important [7].

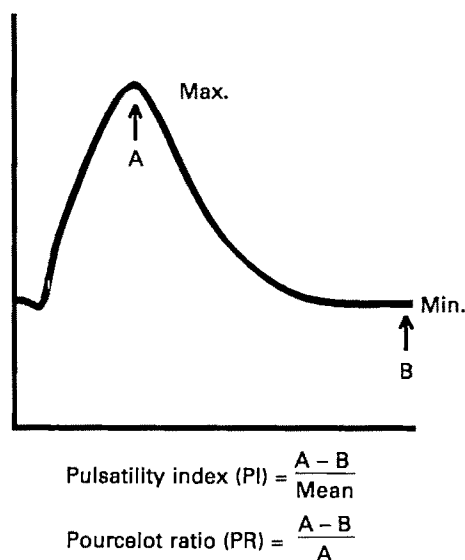
Clinical study of the human placental circulation has presented considerable difficulties, so that the effects of different methods of maternal management and therapy have been extrapolated mainly from animal investigations. Sophisticated studies in pregnant sheep which involve cannulation of the maternal and fetal placental vessels have provided much valuable information about the effects of drugs, stress and biochemical variations [8]. Nevertheless, there is still doubt regarding their relevance to the human because of known inter-species variation.

In the late 1970s, a group of Finnish investigators developed a quantitative method of measurement for both the intervillous and myometrial component of human uterine blood flow, based on the clearance of i.v. xenon-133 [9]. This technique measures the flow per unit volume over an area of 11 cm² of placenta using a single collimator. Jouppila and colleagues [10, 11] used this method to study intervillous blood flow during labour and anaesthesia for elective Caesarean section. While the radiation dose to the mother and fetus is small, this method does not allow instant repetitive investigation of short-lived variation in the maternal circulation, and the placenta must be sited on the anterior uterine wall. Nevertheless, these workers confirmed findings from animal experiments using this technique [10]. As the i.v. xenon-133 method only measures the flow per unit volume of placental tissue over the central area of the placenta, Nylund and colleagues [12] introduced placental scintigraphy using indium-113, which allows total uteroplacental blood flow to be assessed. Again, this method limits the

number of measurements [13] and gives no indication of changes on the fetal side of the placenta.

The ability to examine both sides of the placental circulation simultaneously, continuously and non-invasively has been achieved by the introduction of Doppler ultrasound techniques [14]. Doppler-shifted signals from human blood vessels are within the audible range, thus allowing them to be played through a loudspeaker and stored on an audiotape. These audible signals may be converted to visual signals and real-time spectrum analysis. Equipment is becoming increasingly sophisticated and reliable. Using the colour flow system, real time images are superimposed with blood flow information, coded in colour to indicate directions and velocity of blood flow. Identification of vessels in the uteroplacental and fetoplacental circulations is accurate because of their characteristic flow pattern, and allows their simultaneous recording and quantitative and qualitative estimations to be made. Volume flow is derived from the formula $V\pi r^2$, where V is the time-averaged mean velocity and r is the radius of the vessel. For quantification, the diameter of the vessel must be known and it is assumed that the vessel is circular and the diameter remains constant through the cardiac cycle. As the Doppler shift is directly proportional to the cosine of the angle of *insonation* of the vessel, errors in its measurement cause significant errors in velocity calculation [15]. These inaccuracies in quantifying findings do not affect qualitative flow analysis, as the derived indices are independent of the angle of insonation, while measurement of vessel diameter is not required [16, 17]. The indices, the systolic: diastolic (A:B) ratio, the pulsatility index (PI) and the Pourcelot ratio (PR) (fig. 1) are measures of downstream impedance rather than flow.

Several reports on the use of Doppler waveform analysis in obstetric anaesthesia have been published; two are included in this issue of the Journal [18, 19]. These well-planned studies suggest that extradural anaesthesia with a bupivacaine-adrenaline or lignocaine-adrenaline mixture does not alter placental blood flow or fetal haemodynamics, provided maternal hypotension is prevented by rapid i.v. infusion of crystalloid or administration of ephedrine. However, only eight patients were included in the first study [18] and the timing of the second observation was delayed until a sensory block to T5 had been achieved, which may or may not have coincided with the



A : B ratio = systolic : diastolic ratio

FIG. 1. Definition of three waveform indices.

occurrence of major placental blood flow changes. Only the PR index has normal distribution, which is important in statistical evaluation of the results [20].

In the second study [19], measurements were made before and after the extradural block, during episodes of hypotension and after administration of ephedrine. During episodes of hypotension there were no changes in any index of fetoplacental circulation or fetal outcome.

The comment by Gutsche and Cheek [21] that this method of investigation has revolutionized the practice of obstetrics requires further substantiation, particularly in those situations in which sudden maternal hypotension could reduce placental perfusion during anaesthesia. Correlations of Doppler diagnosed impairment of the placental circulation with other evidence of fetal compromise would do much to enhance its reputation.

J. Moore

REFERENCES

1. Parer JT. Uteroplacental circulation and respiratory gas exchange. In: Shnider SM, Levinson G, eds. *Anaesthesia for Obstetrics*, 2nd Edn. Baltimore: Williams and Wilkins, 1987; 14-21.
2. Greiss FC. Concepts of uterine blood flow. In: Wynn RM, ed. *Obstetrics and Gynecology Annual*. New York: Appleton-Century-Crofts 1973; 55-83.

3. Blanchard K, Dandavino A, Nuwayhid B, Brinkman CR, Assali NS. Systemic and uterine hemodynamic responses to dopamine in pregnant and non-pregnant sheep. *American Journal of Obstetrics and Gynecology* 1978; 130: 669-673.
4. Rankin JHG, McLaughlin MK. The regulation of the placental blood flows. *Journal of Developmental Physiology* 1979; 1: 3-30.
5. Walker AM. Physiological control of the fetal cardiovascular system. In: Beard RW, Nathanieloz PW, eds. *Fetal Physiology and Medicine*, 2nd revised Edn. London: Butterworths, 1984; 287-316.
6. Berman W, Goodling RC, Heymann MA, Rudolph AM. Effects of pharmacologic agents on umbilical blood flow in fetal lambs in utero. *Biology of the Neonate* 1978; 33: 225-235.
7. Hasaart THM, de Haan J, Horiguchi T. Effect of selective occlusion of the umbilical arteries and or venous or uterine blood flow in sheep. *European Journal of Obstetric and Gynaecological Reproduction Biology* 1986; 21: 53-60.
8. Cosmi EV, Shnider SM. Obstetric anesthesia and uterine blood flow. In: Shnider SM, Levinson G, eds. *Anesthesia for Obstetrics*, 2nd Edn. Baltimore: Williams and Wilkins, 1987; 22-40.
9. Rekonen A, Luotola H, Pitkanen M, Kuikka J, Pyorala J. Measurement of intervillous and myometrial blood flow by an intravenous xenon 133 method. *British Journal of Obstetrics and Gynaecology* 1976; 83: 723-728.
10. Jouppila P, Kuikka J, Jouppila R, Holmen A. Effect of induction of general anaesthesia for Caesarean section on intervillous blood flow. *Acta Obstetrica Gynaecologica Scandinavica* 1979; 58: 249-253.
11. Jouppila P, Jouppila R, Holmen A, Korvula A. Lumbar epidural analgesia to improve intervillous blood flow during labor in severe pre-eclampsia. *Obstetrics and Gynecology* 1982; 59: 158-161.
12. Nylund L, Lunell NO, Lewander R, Persson B, Sarby B, Thornstrom S. Uteroplacental blood flow in diabetic pregnancy—measurement with indium 113m and a computer-linked gamma camera. *American Journal of Obstetrics and Gynecology* 1983; 144: 298-302.
13. Skoldebrand A, Eklund J, Johansson H, Lunell H-O, Nylund L, Sarby B, Thornstrom S. Uteroplacental blood flow measured by placental scintigraphy during epidural anaesthesia for Caesarean section. *Acta Anaesthesiologica Scandinavica* 1990; 34: 79-84.
14. McParland P, Pearce, JM. Doppler studies in pregnancy. In: Bonner J, ed. *Recent Advances in Obstetrics and Gynaecology* (16). London: Churchill Livingstone, 1990; 43-73.
15. Griffin D, Cohen-Overbeek T, Campbell S. Fetal and uteroplacental blood flow. *Clinics in Obstetrics and Gynecology* 1983; 10: 565-601.
16. Brar HS, Medearis AL, de Vore GR, Platt LD. Fetal umbilical velocimetry using continuous wave and pulsed wave Doppler ultrasound in high risk pregnancies: a comparison of systolic to diastolic ratios. *Obstetrics and Gynecology* 1988; 72: 607-610.
17. Mehalek KE, Berkowitz GS, Chitkarav V, Rosenberg J, Berkowitz RL. Comparison of continuous wave and pulsed Doppler S/D ratios of umbilical and uterine arteries. *Obstetrics and Gynecology* 1988; 72: 603-606.
18. Alahuhta S, Räsänen J, Jouppila R, Jouppila P, Hollmén AI. Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation. *British Journal of Anaesthesia* 1991; 67: 678-682.
19. McLintic AJ, Danskin FH, Reid JA, Thorburn J. Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the foeto-placental unit during elective Caesarean section. *British Journal of Anaesthesia* 1991; 67: 683-689.
20. Thompson RS, Trudinger BJ, Cook CM. Doppler ultrasound waveform indices: A/B ratio, pulsatility index and Pourcelot ratio. *British Journal of Obstetrics and Gynaecology* 1988; 95: 581-588.
21. Gutsche BB, Cheek TG. Comment. *Survey of Anesthesiology* 1991; 35: 27.

EDITORIAL II

HEADACHE AFTER SPINAL ANAESTHESIA

Since the introduction of spinal anaesthesia by Bier in 1899, headache has remained a well recognized complication but was, initially at least, considered to be a small price to pay for the excellent anaesthesia produced by the spinal block. However, postdural puncture headache (PDPH) may be incapacitating and associated with a substantial increase in postoperative morbidity. Hospital stay may be prolonged and, in addition to headache, there may be rare neurological sequelae, such as III, IV, VI and VIIIth cranial nerve palsies causing diplopia, tinnitus and bilateral deafness [1, 2]. Death resulting from bilateral subdural haematoma associated with PDPH has been described after dural puncture [3].

Not all patients receiving spinal anaesthesia are equally susceptible to PDPH. In 1956, Vandam and Dripps concluded from a large epidemiological study that spinal anaesthesia was safe, but that PDPH was significantly more common in young, female and quickly ambulant patients, with the highest incidence occurring in obstetric patients. The association of PDPH and larger diameter spinal needles was noted also [1].

The cause of PDPH remains unknown, but laboratory and clinical evidence substantiates the most plausible explanation, that CSF leaks at the time of and subsequent to dural puncture [4, 5]. Sitting or standing when the CSF volume is reduced as a result of the leak encourages drainage of the remaining CSF to the lumbar region. The consequent traction on the brain and cortical meninges produces the characteristic headache, which is relieved most commonly by lying down. Reflex cerebrovascular vasodilatation may also cause pain [6].

Thus the two most important factors influencing the frequency and severity of PDPH are the age of the patient and the size of the dural perforation. The shape and size of the hole in the dura is dependent on the diameter of the needle, on the thickness of the dura at the puncture site [7] and on the position of the needle bevel in relation to the long axis of the dural fibres [8]. However, microscopic examination of fresh

cadaver specimens of lumbar dura has shown that the fibres are not uniformly parallel and that their thickness is variable [7, 8]. This variability may explain the conflicting results of clinical and laboratory studies in which the parallel position of the needle bevel in relation to the assumed longitudinal axis of the dural fibres was examined [4, 5, 9–12]. It has been suggested also that a steep angle of penetration of the dura by the needle, in which a longer track is made, may influence the development of PDPH [5].

Classically, PDPH is throbbing in nature, of varying severity and presents most commonly within 48 h of dural puncture. Although usually mild, if severe it may be accompanied by neck stiffness, nausea, vomiting and photophobia. With conservative treatment, spontaneous resolution of the majority of PDPH usually occurs within 1–2 days; occasionally it may last for up to 1 week, but has been reported to persist for 1 year [1, 3, 13, 14]. Conservative treatment includes simple oral and opioid analgesics and a high fluid intake of 1.5–3 litre day⁻¹. Prophylactic 24-h bed rest is ineffective [15], but preliminary reports of the use of i.v. caffeine sodium benzoate 500 mg administered as a 1-litre infusion over 1 h have proved encouraging [6, 16]. The use of an abdominal binder effectively reduces the incidence and severity of headache, but has not proved popular [17, 18].

Severe symptoms may confine the patient to bed and may persist, thereby justifying more invasive methods of treatment. Intermittent injections of physiological saline (60 ml or more) have achieved considerable success in both prophylaxis against and treatment of established PDPH, effectively reducing both its severity and incidence [19, 20]; extradural infusions of Hartmann's solution are also effective [21]. However, the most effective method of treating moderate to severe PDPH is an autologous extradural "blood patch", (EBP) in which, under sterile conditions, 10–20 ml of the patient's blood is withdrawn and injected into the extradural space. First introduced into clinical practice in 1960 [22], use of EBP has now become widespread and the benefit

of blood patching is almost immediate. Studies have confirmed its effectiveness: 89% of PDPH are relieved by the first autologous injection, and a further 8% by a subsequent injection [23]. Long term follow up has confirmed its safety [23, 24]. During the procedure, the patient may complain of paraesthesiae, neckache and backache. After 48 h, back and neckache are common and transient pyrexia may occur [23]. Radicular back pain has been reported, resolving spontaneously [25]. Despite the apparent risk of infection, the procedure appears to be safe, and serious complications are very rare [23, 24, 26].

Postmortem examination of human dura within 48 h of EBP has demonstrated strands of clot attached to the dura [3]. From animal experiments, Di Giovanni, Galbert and Wahle concluded that there was no more tissue reaction after EBP than after simple dural puncture [26]. Although subsequent extradural anaesthesia is usually successful, Rainbird and Pfitzner described restricted extradural spread at repeat Caesarean section with an extradural block which was limited to below L2, 3 years after successful blood patching [27]. Epiarrachidural haematoma has been reported after EBP, but the technique responsible was not routine practice [28]. The volume of blood injected has varied, but the larger the volume the greater the efficacy of the EBP; 18–20 ml is the most common injection volume used.

Prophylactic EBP has been shown to prevent PDPH reliably when the puncture has been made with larger needles such as extradural needles, and has been justified because of the high incidence of PDPH (70%) which require blood patching [29, 30]. Routine use of prophylactic EBP results in some patients unnecessarily receiving an EBP.

Although EBP is an effective treatment for PDPH, it is invasive and unpleasant. In an attempt to reduce the incidence of PDPH after spinal anaesthesia, attention has focused recently on the development and use of very fine spinal needles. Ultra fine needles (30-gauge) have proved difficult to use, identification of CSF is elusive and frequently the spinal block has proved inadequate [31]. Such needles have been regarded as unsuitable for routine use in obstetric patients, although they are associated with headache-free lumbar puncture. Twenty-nine-gauge needles have proved easier to use and have been more successful, with a similar failure rate and a lower

incidence of PDPH than that observed with use of 26-gauge needles (1.4% and 3.7%, respectively [32]). No severe headaches were recorded and no patient required an EBP. Using a 29-gauge needle, Carrie did not observe significant PDPH in 163 obstetric patients [33], but two of the 18 patients in whom a 29-gauge needle was used by Fitzgibbon developed a PDPH which required an EBP [34].

Recently, interest has been rekindled in the use of "blunt" needles in which there is no cutting point, the dural fibres being parted by the rounded but tapering tip of the needle. The 20-gauge Whitacre needle was associated with a lower incidence of PDPH compared with a similar size of Quincke point needle [35, 36]. Laboratory studies have shown that *in vitro* CSF leakages caused by a 22-gauge Whitacre and by a 26-gauge Quincke point needle are similar [4, 5]. These findings have been substantiated by clinical studies [37, 38]. More recently, several smaller diameter Sprotte (24-gauge) and Whitacre (25- and 27-gauge) needles have become available and preliminary clinical studies have confirmed their ability to reduce the incidence of PDPH without compromising the ease of administration of spinal anaesthesia [39–41]. In this issue, Lynch and colleagues report on the low incidence of PDPH after use of 25- and 22-gauge Whitacre needles [42]. The incidence of headache was reduced in association with the finer gauge needles, but the difference was not statistically significant.

Clearly, PDPH is an undesirable complication to be avoided if possible. All patients undergoing spinal anaesthesia must be informed of the risks of PDPH and that safe and effective treatment exists, should one develop. No patient should be subjected to PDPH for more than 24 h without the anaesthetist being informed and EBP being considered. PDPH is a confusing entity as there are no universally agreed definitions and different investigators apply different criteria. To confirm the benefits of the use of fine, pencil-point needles, subsequent studies must define the PDPH clearly in terms of duration and severity and be applied to a population at equal risk of headache. Large numbers of patients should be studied because of the expected low incidence of PDPH associated with currently available needles. It may transpire that, in routine clinical practice, pencil-point needles will combine the strength and "feel" of the larger needle with the negligible incidence of

PDPH associated with the fine, 29-gauge Quincke point needle.

J. A. Reid and J. Thorburn

REFERENCES

- Vandam LD, Dripps RD. Long term follow up of patients who received 10,098 spinal anesthetics. Syndrome of decreased intracranial pressure (headache and ocular and auditory difficulties). *Journal of the American Medical Association* 1956; 161: 586-591.
- Wang LP, Fog J, Bore M. Transient hearing loss following spinal anaesthesia. *Anaesthesia* 1987; 42: 1258-1263.
- Endelman JD, Wingard DW. Subdural hematomas after lumbar puncture. *Anesthesiology* 1980; 52: 166-167.
- Cruikshank RH, Hopkinson JM. Fluid flow through dural puncture sites. An *in vitro* comparison of needle point types. *Anaesthesia* 1989; 44: 415-418.
- Ready LB, Cuplin S, Haschke RH, Nessly M. Spinal needle determinants of rate of transdural fluid leak. *Anesthesia and Analgesia* 1989; 69: 457-460.
- Sechzer PH. Post spinal anaesthesia headache treated with caffeine II. Intracranial vascular distension a key factor. *Current Therapeutic Research* 1979; 26: 440-448.
- Dittman H, Schäfer HG, Ulrich J, Bond-Taylor W. Anatomical re-evaluation of lumbar dura mater with regard to post spinal headache. Effect of dural puncture. *Anaesthesia* 1988; 43: 635-637.
- Fink BR, Walker S. Orientation of fibres in human dorsal lumbar dura mater in relation to lumbar puncture. *Anesthesia and Analgesia* 1989; 69: 768-772.
- Dooner JJ. Needle bevel direction and post lumbar puncture headache. *Anesthesiology* 1989; 71: 623-624.
- Mihic DN. Post spinal headache and relationship of needle bevel to longitudinal dural fibres. *Regional Anaesthesia* 1985; 10: 76-81.
- Lybecker H, Moller JT, May O, Nielson HK. Incidence and prediction of post dural puncture headache. A prospective study of 1021 spinal anesthetics. *Anesthesia and Analgesia* 1990; 70: 389-394.
- Norris M, Leighton B, De Simone L. Needle bevel direction and headache after inadvertent dural puncture. *Anesthesiology* 1989; 70: 729-731.
- Brown BA, Jones OW. Prolonged headache following spinal puncture. Response to surgical treatment. *Journal of Neurology* 1962; 19: 349-350.
- Cast W, Edlist G. Post spinal headache, successful epidural blood patch eleven weeks after onset. *Journal of the American Medical Association* 1974; 227: 786-787.
- Thornberry EA, Thomas TA. Posture and post-spinal headache. A controlled trial in 80 obstetric patients. *British Journal of Anaesthesia* 1988; 60: 196-197.
- Jarvis AP, Greenawalt JW, Fagraeus L. Intravenous caffeine for post dural puncture headache. *Anesthesia and Analgesia* 1986; 65: 316-317.
- Beck WW. Prevention of post partum spinal headache. *American Journal of Obstetrics and Gynecology* 1973; 115: 334-356.
- Mosavy SH, Shafei M. Prevention of headache consequent on dural puncture in obstetric patients. *Anaesthesia* 1975; 30: 807-809.
- Rice GG, Dabbs CH. The use of peridural and subarachnoid injections of saline solution in the treatment of severe post spinal headache. *Anesthesiology* 1950; 11: 17-23.
- Craft JB, Epstein BS, Coakley CS. Prophylaxis of dural puncture headache with epidural saline. *Anesthesia and Analgesia* 1973; 52: 228-231.
- Crawford JS. The prevention of headache consequent on dural puncture. *British Journal of Anaesthesia* 1972; 44: 598-600.
- Gormley JB. Treatment of post spinal headache. *Anesthesiology* 1960; 21: 565-566.
- Abouleish E, de la Vega S, Blendinger I, Trio T. Long term follow up of epidural blood patch. *Anesthesia and Analgesia* 1975; 54: 459-463.
- Crawford JS. Experiences with epidural blood patch. *Anaesthesia* 1980; 35: 513-515.
- Shantha TR, McWhirter WR. Complications following epidural 'blood patch' for lumbar puncture headache. *Anesthesia and Analgesia* 1973; 52: 67-72.
- Di Giovanni AJ, Galbert NW, Wahle WM. Epidural injection of autologous blood for post lumbar puncture headache. Additional clinical experiences and laboratory investigation. *Anesthesia and Analgesia* 1972; 51: 226-232.
- Rainbird A, Pfizner A. A restricted spread of analgesia following epidural blood patch. *Anaesthesia* 1983; 38: 481-484.
- Reynolds AF jr, Hammeroff SR, Blitt CD, Roberts WL. Spinal and subdural epirachnoid hematoma: a complication of a novel epidural blood patch. *Anesthesia and Analgesia* 1980; 59: 702-703.
- Cheek TG, Banner R, Sauter J, Gutsche BB. Prophylactic extradural blood patch is effective. *British Journal of Anaesthesia* 1988; 61: 340-342.
- Colanno-Romano P, Shapiro BE. Prophylactic epidural blood patch in obstetrics. *Anesthesiology* 1988; 69: A665.
- Lesser P, Bembridge M, Lyons G, MacDonald R. An evaluation of a 30-gauge spinal needle for spinal anaesthesia for Caesarean section. *Anaesthesia* 1990; 45: 767-768.
- Dittman M, Renkl F. Spinal anesthesia with extremely fine needles. *Anesthesiology* 1989; 70: 1035-1036.
- Carrie LES, Collins PD. 29-gauge spinal needles. *British Journal of Anaesthesia* 1991; 66: 145-146.
- Fitzgibbon D, Gardiner J. Post dural puncture headache with 29 gauge spinal needles. *Anaesthesia* 1990; 45: 593.
- Hart JR, Whitacre RJ. Pencil point needles in prevention of post spinal headache. *Journal of the American Medical Association* 1951; 147: 657-658.
- Haraldson S. Headache after spinal anesthesia: experiments with a new spinal needle. *Anesthesiology* 1951; 12: 321-327.
- Sami HM, Skaredoff MN. In hospital incidence of post lumbar puncture headache (PLPH) in Cesarean section patients associated with the 22-gauge Whitacre needle. *Anesthesiology* 1989; 71: A861.
- Snyder GE, Person DL, Flor CE, Wilden RT. Headache in obstetrical patients: comparison of Whitacre needle versus Quincke needle. *Anesthesiology* 1989; 71: A860.
- Hurley RJ, Hertwig LM, Johnson MD, Datta S. Incidence of post dural puncture headache in the obstetric patient: 25-gauge Whitacre versus 26-gauge Quincke tip needles. A preliminary report. European Society of Regional Anaesthesia Meeting, Athens 1991.
- Cesarini M, Torielli R, Lahaye F, Mene JH, Cabiro L. Sprotte needle for intrathecal anaesthesia for Caesarean

- section: incidence of postdural puncture headache. *Anaesthesia* 1990; 45: 656-658.
41. Sprotte G, Schedel R, Pajunk H, Pajunk H. Eine atraumatische universalkanule fuer einzeitige regionalanaesthesien. *Regional Anaesthesia* 1987; 10: 104-108.
42. Lynch J, Krings-Ernest I, Strick K, Topalidis K, Schaaf H, Fiebig M. Use of a 25-gauge Whitacre needle to reduce the incidence of postdural puncture headache. *British Journal of Anaesthesia* 1991; 67: 690-693.

EFFECTS OF EXTRADURAL BUPIVACAINE WITH ADRENALINE FOR CAESAREAN SECTION ON UTEROPLACENTAL AND FETAL CIRCULATION

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SUMMARY

We have studied the effects of an extradural block using bupivacaine with adrenaline 90–100 µg on blood flow in the maternal uterine and placental arcuate arteries and the fetal umbilical, renal and middle cerebral arteries, using a colour Doppler technique in eight healthy parturients undergoing elective Caesarean section. Fetal myocardial function was investigated simultaneously by M-mode echocardiography. Maternal heart rate increased and diastolic arterial pressure decreased after extradural administration of bupivacaine with adrenaline. The latter effect was relieved by increasing the infusion rate in every case and none of the patients required vaso-pressors. There were no significant differences in maternal or fetal blood velocity waveforms, and no significant changes were found in any of the fetal myocardial measurements relative to control values. These observations suggest that extradural anaesthesia using bupivacaine with adrenaline does not have an adverse effect on vascular resistance in the uteroplacental or fetal circulations or on fetal myocardial function in normal pregnancy when bupivacaine–adrenaline is administered fractionally and maternal hypotension is prevented by rapid crystalloid volume loading.

KEY WORDS

Anaesthesia, obstetric: Caesarean section. Anaesthetic technique: extradural. Measurement techniques: Doppler ultrasonics, echocardiography. Placenta: blood flow velocity. Uterus: blood flow, adrenaline.

been reported to prolong the duration of analgesia and to delay maternal hypotension and reduce its degree [2]. Although no clinical study in humans has demonstrated deleterious effects on the fetus or the neonate, systemic absorption of adrenaline from the extradural space may reduce uteroplacental blood flow [3, 4]. A small i.v. bolus of adrenaline is associated with reductions in uterine blood flow in pregnant sheep [5]. We have examined, therefore, the effects of an extradural block using bupivacaine with adrenaline for elective Caesarean section on blood flow velocity waveforms in uteroplacental and fetal vessels and simultaneously assessed fetal myocardial function by M-mode echocardiography.

PATIENTS AND METHODS

After approval from the local Ethics Committee and informed patient consent, we studied eight parturients at term scheduled for elective Caesarean section under extradural anaesthesia. All were healthy, had an uncomplicated singleton pregnancy and were to be delivered by Caesarean section because of fetal breech presentation or fetopelvic disproportion.

Before the first ultrasound examination in the operating theatre, an extradural catheter was inserted via the L2–3 or L3–4 interspace with the patient in the left lateral position. No local anaesthetic solution was injected. Oxygen

The addition of adrenaline to extradural bupivacaine for Caesarean section may improve the quality of the block [1]. Extradural adrenaline has

This article is accompanied by Editorial I.

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3 litre min^{-1} was administered via a mask (Hudson). Maternal ECG was monitored continuously and arterial pressure and heart rate were recorded at 5-min intervals using an automated non-invasive arterial pressure monitor.

The first ultrasound measurement, with a Toshiba SSA-270 colour Doppler instrument with a 3.75-MHz sector probe, was performed before prehydration; the technique has been described in detail previously [6]. Pulsatility indices (PI) were derived for the blood velocity waveforms of the maternal uterine artery (main branch on the placental side of the uterus), the placental arcuate artery and the fetal umbilical, middle cerebral and renal arteries. The fetal heart rate was derived from the umbilical Doppler signal.

An M-mode echocardiographic examination was performed by directing the transducer perpendicular to the ventricular septum and positioning the M-line through the chambers at the level of the atrioventricular valves. The end-systolic (ES) and end-diastolic (ED) inner diameters of the ventricles were measured and the fractional shortenings of the ventricles $((\text{ED} - \text{ES})/\text{ED})$ were calculated. Mean circumferential shortenings of the ventricles were calculated from the fractional shortenings $((\text{ED} - \text{ES})/\text{ED} \times \text{duration of systole})$. The inner end-diastolic dimension was used to determine the size of the fetal heart, and fractional and mean circumferential shortenings of the ventricles were obtained to evaluate the functional properties of the heart. The pulmonary trunk and ascending aorta of the fetus were identified by colour Doppler in short axis and five chamber views. The systolic peak velocities in the pulmonary artery and the aorta were measured by means of the pulsed Doppler system at a point immediately distal to the valve leaflets. Only an angle of less than 5° between the direction of the transducer beam and the estimated direction of flow was regarded as acceptable. Each series of measurements took an average of 25 min (range 19–33 min) and were performed by the same obstetrician (J.R.). All the blood flow velocity waveform recordings were obtained during periods of fetal rest without breathing movements with the mother in a semi-left lateral position.

Before the extradural test dose, 1 litre of balanced electrolyte solution (Ringersteril, Medipolar, Finland) was infused rapidly i.v.; while the full dose of commercially available 0.5 % bupivacaine with adrenaline 1:200 000 was

taking effect, a further 1 litre of electrolyte solution was infused. The time needed for the infusion of 2 litre of preload solution was recorded.

Bupivacaine–adrenaline was injected fractionally in order to reach the T5 level. In four patients in whom the height of the block was below T5 after 20 ml of 0.5 % bupivacaine with adrenaline, an additional dose of 0.5 % plain bupivacaine was given.

Maternal arterial pressure was measured every 2 min from induction until delivery. Maternal hypotension, defined as a reduction in systolic arterial pressure of more than 30 mm Hg relative to the control value (minimum systolic arterial pressure recorded in the operating theatre before preloading) or a systolic arterial pressure of less than 100 mm Hg, was treated by increasing the infusion. When sensory analgesia had reached the T5 level the ultrasound examination was repeated by the same methods and with the same targets as at the control stage. Each patient provided her own baseline readings. At delivery, Apgar scores were noted and samples of umbilical arterial and venous blood were taken for the measurement of acid–base status.

Data were analysed with a Macintosh II computer using the Stat View 512+ statistical package. Student's *t* test for paired data was used. The analysis was two-tailed, and $P < 0.05$ was considered statistically significant. Values are expressed as mean (SD).

RESULTS

One of the women had to be given a general anaesthetic after skin incision and before the abdominal cavity was entered. The perinatal data on her offspring were excluded.

One of the patients was given adrenaline 125 μg in the bupivacaine solution by mistake, while for all the other patients the dose varied between 90 and 100 μg . The total amount of bupivacaine administered was 113.7 mg (range 90–135 mg). The first 1 litre of electrolyte solution was infused in 11 min (range 8–14 min) and the second in 44 min (range 20–63 min).

Mean maternal diastolic arterial pressure was less than the control value throughout the period studied. The maximum reduction in diastolic arterial pressure, which was also significant, occurred during the establishment of extradural block (table I). There was no significant change in

TABLE I. Maternal haemodynamics data. Smallest values (mean SD) before prehydration (control) (1), during the establishment of extradural anaesthesia (2), and at the beginning of (3) and during (4) the second Doppler examination. P values indicate significance of difference from control measurement

	1	P	2	P	3	P	4
Systolic arterial pressure (mm Hg)	129 (13.5)	0.125	120 (11.3)	0.953	129 (12.8)	0.452	118 (11.1)
Diastolic arterial pressure (mm Hg)	75 (8.6)	0.015	62 (9.9)	0.090	64 (15.6)	0.086	65 (14.1)
Maternal heart rate (beat min ⁻¹)	77 (12.0)	0.233	81 (12.4)	0.018	87 (12.3)	0.375	80 (11.0)

TABLE II. Mean (SD) fetal heart rate and blood velocity wave-form indices (pulsatility index) for the maternal uterine, placental arcuate and fetal umbilical, middle cerebral and renal arteries before and after extradural anaesthesia with bupivacaine containing adrenaline

	Before extradural	After extradural	P
Fetal heart rate (beat min ⁻¹)	138 (13.4)	132 (14.8)	0.286
Pulsatility index			
Uterine artery	0.75 (0.19)	0.83 (0.18)	0.193
Arcuate artery	0.45 (0.90)	0.47 (0.75)	0.756
Umbilical artery	0.81 (0.17)	0.84 (0.18)	0.635
Middle cerebral artery	1.36 (0.28)	1.36 (0.21)	0.919
Renal artery	2.15 (0.35)	1.97 (0.27)	0.319

mean maternal systolic arterial pressure. None of the patients became hypotensive or received a vasopressor drug. Mean maternal heart rate increased during the procedure, the change being greatest, and also significant, at the beginning of the second ultrasound examination (table I).

Mean maternal uterine, placental arcuate and fetal umbilical PI values and mean PI for the fetal renal or middle cerebral artery did not change significantly at any time (table II). There were no significant differences relative to control values in any fetal myocardial measurement. The systolic peak velocities of the pulmonary trunk and ascending aorta remained stable throughout. There was no change in the mean fetal heart rate after extradural anaesthesia with bupivacaine containing adrenaline (table III).

The mean birth weight of the neonates was 3718 (762) g. All had Apgar scores of 9 or 10 at 5 min. The smallest pH values in the umbilical venous and arterial blood were 7.36 and 7.24, respectively.

DISCUSSION

The advent of colour Doppler techniques, providing a non-invasive method for locating the uterine and fetal vessels exactly, has enabled reliable, detailed evaluation of the haemodynamics of maternal-fetal-placental units and

TABLE III. Changes in fetal myocardial contractility and in ventricular sizes (mean (SD)) before and after extradural anaesthesia with bupivacaine containing adrenaline. IDD = inner end-diastolic dimension

	Before extradural	After extradural	P
Left ventricle			
Fractional shortening (%)	33.6 (3.1)	34.6 (3.8)	0.517
Mean circumferential shortening (circ s ⁻¹)	1.31 (0.16)	1.35 (0.19)	0.407
IDD (mm)	18.5 (1.7)	19.1 (2.0)	0.145
Right ventricle			
Fractional shortening (%)	30.4 (2.0)	28.6 (3.3)	0.111
Mean circumferential shortening (circ s ⁻¹)	1.16 (0.15)	1.06 (0.18)	0.121
IDD (mm)	19.2 (2.7)	19.2 (1.6)	0.983
Pulmonary trunk			
Systolic peak velocity (cm s ⁻¹)	80.9 (11.2)	74.3 (11.1)	0.065
Ascending aorta			
Systolic peak velocity (cm s ⁻¹)	94.0 (15.5)	90.5 (15.6)	0.239

short-term alterations in this respect. The recording of blood velocity waveforms in these vessels enables comprehensive simultaneous measurement of the uteroplacental and fetal circulation systems. Special indices such as PI, as used here, correlate directly with peripheral vascular resistance [7]. Technical improvements have also made it possible to image the fetal heart by real-time-directed M-mode echocardiography and obtain information on fetal myocardial contractility and ventricular size [8]. The present study involved the simultaneous evaluation of maternal uterine blood flow velocity and fetal haemodynamics during extradural anaesthesia in as comprehensive a manner as possible using modern Doppler technology.

The results show that extradural bupivacaine with adrenaline for elective Caesarean section in healthy parturients did not alter uteroplacental or fetal haemodynamics. Using functional placental scintigraphy, Skjöldebrand and co-workers [3] demonstrated a median decrease of 34% in placental blood flow after extradural bupivacaine-adrenaline. This method measures the uteroplacental blood flow volume, while the Doppler method measures vascular resistance in the uterine arteries. Both have been validated in several clinical studies, but to our knowledge they have not been compared.

There are also differences in anaesthetic management between these two series which may explain the conflicting results. First, Skjöldebrand and others gave 10 ml/kg body weight of balanced electrolyte solution as a preload while we used approximately 25 ml/kg body weight; second, we performed the infusion more rapidly to achieve maximal expansion in plasma volume. A recommended fluid load before instituting regional block for Caesarean section is 1000–2000 ml [9], or at least 30% of the calculated pregnant blood volume—at least 1500 ml [10]. Third, although the doses of adrenaline used by Skjöldebrand and colleagues were smaller (45–55 µg *vs* 90–100 µg) they administered the main dose of bupivacaine (15 or 19 ml) with adrenaline (37.5 or 47.5 µg) by rapid bolus injection, while we gave it in fractional amounts. Our results are consistent with some other previous reports, however, in that there were no changes in either uterine or umbilical artery blood flow waveforms after extradural lignocaine-adrenaline [11], the indices of umbilical artery waveforms remained unchanged when chlorprocaine was used with adrenaline

[12] and an increase in blood flow in the fetal descending aorta was reported by Lindblad and colleagues after extradural bupivacaine containing adrenaline, but no change after etidocaine with adrenaline [13]. In all these cases the volume of crystalloid solution administered was at least 1500 ml.

The decrease in maternal diastolic arterial pressure observed here occurred before completion of administration of local anaesthetic, whereas the maximal increase in maternal heart rate took place later, just before the second ultrasound examination. These changes could result not only from the extradural block itself but from the beta-adrenergic effects of the adrenaline added to the local anaesthetic solution. The beta-adrenergic stimulation produced by a low adrenaline concentration reduces peripheral resistance and increases heart rate because of direct cardiac stimulation and increased venous return [14]. In a recent study, beta-2 mediated vasodilatation was found after extradural bupivacaine with adrenaline for Caesarean section without any significant changes in maternal heart rate or cardiac output [15]. The cardiovascular effects of adrenaline occur shortly after extradural injection and last for 60 min [16]. Our results conform with these observations.

We did not measure maternal or cord blood catecholamine concentrations. Maternal plasma concentrations of adrenaline have been reported previously to be increased relative to the antepartum values [17] during elective Caesarean section (without antecedent labour) under extradural anaesthesia with an adrenaline-free agent. Adrenaline concentrations decreased during extradural Caesarean section when the control values were taken as those recorded immediately before administration of the extradural block [18]. Previous research has demonstrated the presence of catecholamine-metabolizing enzymes, monoamine oxidase [19] and catechol-O-methyltransferase [20], in the human placenta, the activity of the last of these being 20-fold at the maternal surface of the placenta compared with that of the fetus [21], indicating that these enzymes seem to play a role in defending the fetus from maternal circulating catecholamines. Our finding that adrenaline given to a mother with an uncomplicated pregnancy has no effect on the fetus is in agreement with these findings.

There is concern that systemic absorption of the adrenaline added to extradural bupivacaine

for Caesarean section may reduce uteroplacental blood flow, but the present results suggest that it has no adverse effects on vascular resistance in the uteroplacental and fetal circulations or in fetal myocardial function if bupivacaine-adrenaline is administered fractionally and if an anaesthetic technique is used with sufficient volume loading.

REFERENCES

1. Laishley RS, Morgan BM. A single dose epidural technique for Caesarean section. *Anaesthesia* 1988; 43: 100-103.
2. Wilson CM, Moore J, Ghaly RG, Flynn R, McClean E, Dundee JW. Plasma concentrations of bupivacaine during extradural anaesthesia for Caesarean section. *Anaesthesia* 1988; 43: 12-15.
3. Skjöldebrand A, Eklund J, Lunell N-O, Nylund L, Sarby B, Thornström S. The effect on uteroplacental blood flow of epidural anaesthesia containing adrenaline for Caesarean section. *Acta Anaesthesiologica Scandinavica* 1990; 34: 85-89.
4. Joupila R, Joupila P, Kuikka J, Hollmén A. Placental blood flow during Caesarean section under lumbar extradural analgesia. *British Journal of Anaesthesia* 1978; 50: 275-279.
5. Hood DD, Dewan DM, James FM III. Maternal and fetal effects of epinephrine in gravid ewes. *Anesthesiology* 1986; 64: 610-613.
6. Alahuhta S, Räsänen J, Joupila R, Joupila P, Kangas-Saarela T, Hollmén AI. Uteroplacental and fetal haemodynamics during extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1991; 66: 319-323.
7. Trudinger BJ, Stevens D, Connelly A, Hales JRS, Alexander G, Bradley L, Fawcett A, Thompson RS. Umbilical artery flow velocity waveforms and placental resistance: The effects of embolization of the umbilical circulation. *American Journal of Obstetrics and Gynecology* 1987; 157: 1443-1448.
8. DeVore GR, Siassi B, Platt LD. M-mode assessment of ventricular size and contractility during the second and third trimesters of pregnancy in the normal fetus. *American Journal of Obstetrics and Gynecology* 1984; 150: 981-988.
9. Shnider SM, Levinson G. Anesthesia for Cesarean section. In: Shnider SM, Levinson G, eds. *Anesthesia for Obstetrics*. Baltimore: Williams & Wilkins, 1987; 159-178.
10. Bassell GM. Anesthesia for cesarean section. *Clinical Obstetrics and Gynecology* 1985; 28: 722-734.
11. Morrow RJ, Rolbin SH, Ritchie JWK, Haley S. Epidural anaesthesia and blood flow velocity in mother and fetus. *Canadian Journal of Anaesthesia* 1989; 36: 519-522.
12. Veille JC, Youngstrom P, Kanaan C, Wilson B. Human umbilical artery flow velocity waveforms before and after regional anesthesia for cesarean section. *Obstetrics and Gynecology* 1988; 72: 890-893.
13. Lindblad A, Bernow J, Vernerström E, Maršal K. Effects of extradural anaesthesia on human fetal blood flow in utero. *British Journal of Anaesthesia* 1987; 59: 1265-1272.
14. Weiner N. Norepinephrine, epinephrine, and the sympathomimetic amines. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *The Pharmacological Basis of Therapeutics*. New York: MacMillan, 1985; 145-180.
15. Grant GJ, Ramanathan S, Turndorf H. The maternal haemodynamic effects of bupivacaine-epinephrine mixture used for obstetrical anaesthesia. *Acta Anaesthesiologica Scandinavica* 1990; 34: 543-547.
16. Abboud TK, David S, Nagappala S, Costandi J, Yanagi T, Haroutunian S, Yeh SU. Maternal, fetal, and neonatal effects of lidocaine with and without epinephrine for epidural anesthesia in obstetrics. *Anesthesia and Analgesia* 1984; 63: 973-979.
17. Jones CM III, Greiss FC jr. The effect of labor on maternal and fetal circulating catecholamines. *American Journal of Obstetrics and Gynecology* 1982; 144: 149-153.
18. Loughran PG, Moore J, Dundee JW. Maternal stress response associated with Caesarean delivery under general and epidural anaesthesia. *British Journal of Obstetrics and Gynaecology* 1986; 93: 943-949.
19. Thompson RHS, Tickner A. Observations on the monoamine oxidase activity of placenta and uterus. *Biochemical Journal* 1949; 45: 125-130.
20. Iisalo E, Castren O. The enzymatic inactivation of noradrenaline in human placental tissue. *Annales Medicinæ Experimentalis et Biologiae Fenniae* 1967; 45: 253-257.
21. Barnea ER, Fakih H, Oelsner G, Walner S, DeCherney AH, Naftolin F. Effect of antihypertensive drugs on catechol-O-methyltransferase and monoamine oxidase activity in human term placental explants. *Gynecologic and Obstetric Investigation* 1986; 21: 124-130.

EFFECT OF ADRENALINE ON EXTRADURAL ANAESTHESIA, PLASMA LIGNOCAINE CONCENTRATIONS AND THE FETO-PLACENTAL UNIT DURING ELECTIVE CAESAREAN SECTION

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SUMMARY

Extradural anaesthesia was induced with either 2% lignocaine or 2% lignocaine with adrenaline 1:200 000 in 20 patients undergoing elective Caesarean section. With the adrenaline-containing solution, a smaller dose of lignocaine was required to produce an adequate block and the lignocaine concentrations in both mother and neonate were significantly smaller compared with the plain solution. Arterial pressures were less in the adrenaline group, but there was no difference in umbilical flow velocity waveform, fetal heart rate or fetal outcome. Neither feto-placental circulation nor fetal outcome were affected adversely by episodes of hypotension or the ephedrine used for treatment.

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural. Placenta: umbilical blood flow.

Although bupivacaine is the agent used most commonly for Caesarean section under extradural anaesthesia in the U.K., lignocaine has been shown to be an effective alternative and confers certain advantages over bupivacaine in this context [1]. With a lower pK_a , lignocaine has a shorter latency of effect which facilitates dose titration and reduces preoperative preparation time [1, 2]. In addition, intractable cardiovascular toxicity has not been associated with the use of lignocaine, but is an important toxic effect of bupivacaine [3]. It has been shown, in contexts other than Caesarean section, that the efficacy of extradural lignocaine may be improved further if an adrenaline-containing solution is used [4-6]. The aim of this study was to determine if a lignocaine and adrenaline solution has advantages

over a plain lignocaine solution when used to provide extradural anaesthesia for Caesarean section. The comparison between the techniques was made in terms of anaesthetic characteristics, plasma concentrations of lignocaine, maternal and fetal haemodynamics and fetal outcome.

PATIENTS AND METHODS

We studied 20 healthy women undergoing elective Caesarean section. The study was approved by the Ethics Committee of The Queen Mother's Hospital and all patients gave informed consent. The indication for elective Caesarean section was either repeat Caesarean section or breech presentation. There was no evidence of preoperative fetal compromise or maternal disease.

Patients were given ranitidine 150 mg by mouth on the evening before and on the morning of surgery. Before extradural anaesthesia was induced, patients were pre-loaded with Hartmann's solution 1 litre. They were then allocated randomly to receive either 2% plain lignocaine (group A; $n = 10$) or 2% lignocaine with adrenaline 1:200 000 (group B; $n = 10$). Both patient and investigator were blind to the identity of the solution used. With the patient in either the sitting or lateral position, a 20-gauge extradural catheter was inserted via an 18-gauge Tuohy needle at L3-4. The extradural space was ident-

This article is accompanied by Editorial 1.

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ified using loss of resistance with local analgesia comprising 0.5% prilocaine 2 ml. Extradural block was then induced with the patient in the left lateral position. An initial test dose of 3 ml of the allocated solution was followed by a 10-ml dose after 5 min. At 5-min intervals thereafter the level of anaesthesia to pinprick was assessed and further increments given according to the extent of spread. This was continued until an adequate block was achieved (loss of pinprick sensation from S5 to T6 bilaterally). The time taken to achieve an adequate block (measured from the time of test dose), the total dose of lignocaine used to produce the block, and the time at which further analgesia was required were recorded.

Arterial pressure and heart rate were measured using a 2200 I Datascope at 1-min intervals from the time of catheter insertion. The incidence of significant hypotension (systolic arterial pressure ≤ 90 mm Hg) was noted. Hypotension was treated by increasing the rate of infusion and, if necessary, by a bolus dose of ephedrine 6 mg.

The feto-placental circulation was assessed using Doppler velocimetry. When placental vascular resistance increases, the umbilical artery flow decreases [7]. This is reflected in a reduction in diastolic flow velocity and Doppler frequency. The resulting changes in the umbilical arterial flow velocity waveform may be assessed quantitatively by measuring the peak systolic: minimum diastolic velocity ratio (A:B ratio) and the pulsatility index (PI) (fig. 1). An increase in one of these values reflects an increase in flow resistance within the vascular bed distal to the site

of measurement [7, 8]. As the end-diastolic velocity varies with fetal heart rate (FHR), changes in the A:B ratio may reflect changes in FHR and changes in placental resistance [9]. Therefore, A:B ratios were corrected for FHR using a modal heart rate of 140 beat min^{-1} and the method described by Mires and colleagues [9]. As the importance of this correction is contentious when the FHR is within normal limits, results are given in both corrected and uncorrected forms [10].

Studies were performed using a Doptek 4-MHz continuous wave Doppler system with on-line spectral analysis. Measurements were made with the patient in the modified supine position. The umbilical artery was located using two-dimensional ultrasonography. The Doppler transducer was orientated so that the umbilical arterial signal had maximum amplitude and minimum artefact and could be displayed together with the venous trace. Five consecutive waveforms were recorded at the following times: before insertion of the extradural catheter, immediately before Caesarean section, during episodes of hypotension and after administration of ephedrine. Calculation of the mean A:B ratios, PI and FHR were carried out using on-board custom-written software.

Maternal venous blood samples were taken from the non-infusion arm before the test dose, at 10-min intervals from the time at which an adequate block was achieved and immediately after delivery. Umbilical arterial and venous blood samples were taken immediately after delivery for blood-gas and plasma lignocaine analysis. Samples for lignocaine assay were stored at 4 °C after centrifugation and plasma separation. Lignocaine assay was carried out by a solvent extraction method using high pressure liquid chromatography [11]. Neonatal Apgar scores were recorded at 1 min and 5 min.

Statistics

Statistical evaluation of the data was carried out using the Minitabs Release 7.1 statistical package. Data were analysed by Student's *t* test, chi-square and Mann-Whitney *U* test where appropriate. $P < 0.05$ was considered significant. Values are expressed as mean (SD).

RESULTS

One patient in group B required spinal anaesthesia after failure to achieve a level of block above T10. Her results were not included in the analysis.

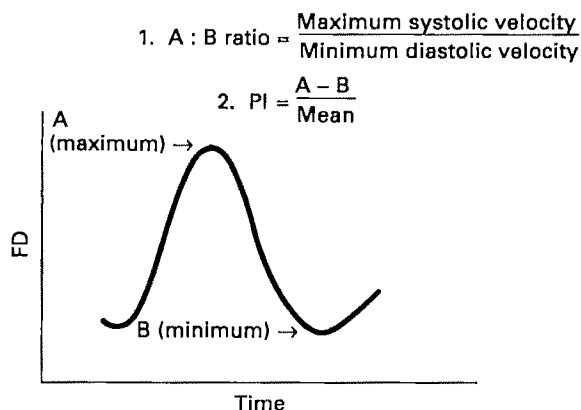


FIG. 1. Characteristic umbilical artery flow velocity waveform showing derivation of A:B ratio and pulsatility index (PI). The Doppler frequency shift (FD) is directly proportional to flow velocity.

TABLE I. Patient characteristics (mean (range or SD)). No significant differences between groups

	n	Age (yr)	Gestation (weeks)	Weight (kg)	Height (m)
2% Lignocaine	10	29.0 (19-37)	38.4 (0.88)	55.3 (8.44)	1.59 (0.05)
2% Lignocaine + adrenaline	9	29.3 (17-37)	38.8 (1.32)	62.1 (13.95)	1.62 (0.09)

TABLE II. Characteristics of extradural anaesthesia. Mean (SD or, median and range)

	2% Lignocaine (n = 10)	2% Lignocaine + adrenaline (n = 9)	P
Dose required (mg)	493 (64.2)	400 (108)	< 0.05
Onset time (min)	35.8 (17.00)	29.9 (9.14)	ns
Time to further analgesia (min)	92.9 (86; 11-220)	237 (100; 12-694)	ns

TABLE III. Mean (SD) maternal and umbilical vein plasma concentrations of lignocaine, and plasma lignocaine concentration (mg litre⁻¹): dose (mg) ratio calculated using peak (30 min) plasma concentration of lignocaine

	Lignocaine concn ($\mu\text{g ml}^{-1}$)				Umbilical vein	Umbilical vein: maternal vein ratio	Plasma concn: dose ratio
	Time after onset (min)						
	10	20	30	40			
2% Lignocaine ($n = 10$)	1.309 (0.521)	1.715 (0.660)	2.22 (0.556)	2.03 (0.649)	1.411 (0.573)	0.600 (0.17)	0.0047 (0.0012)
2% Lignocaine +adrenaline ($n = 9$)	0.542 (0.349)	0.854 (0.511)	1.317 (0.570)	0.78	0.804 (0.370)	0.605 (0.29)	0.0034 (0.0012)
<i>P</i>	< 0.005	< 0.005	< 0.02	—	< 0.02	ns	< 0.024

There was no significant difference in the mean age, weight, height or gestation of the patients in the two groups (table I). The mean dose of lignocaine required to produce an adequate block in group A was 493 (SD 64.2) mg; this was significantly greater than that required in group B (400 (108) mg) ($P < 0.05$). The mean time taken to produce an adequate block in each group was 35.8 (17.0) min in group A and 29.9 (9.14) min in group B (ns). The mean time interval between establishing an adequate block and the first analgesia requirements was 92.9 min (median 86 min, range 11-220 min) in group A and 237 min (median 100 min, range 12-694 min) in group B (ns) (table II).

Plasma concentrations of lignocaine were significantly greater in group A at each time interval, except at 40 min where there were insufficient numbers in group B to make statistical comparison

(table III). Umbilical venous plasma concentrations were also significantly greater in group A (1.411 (0.573) µg ml⁻¹ compared with 0.804 (0.370) µg ml⁻¹ ($P < 0.02$)). There was no difference in the umbilical venous to maternal venous lignocaine concentration ratio between the two groups. The peak plasma lignocaine concentration: dose ratio was significantly greater in group A than in group B (0.0047:1 (0.0012) vs 0.0034:1 (0.0012) ($P < 0.024$)).

Systolic and diastolic arterial pressures in group A were greater than those in group B, although the difference reached significance only at 15 min (fig. 2). There was no significant difference in the incidence or duration of systolic hypotension of 90 mm Hg or less (six patients in group A with a mean duration of 2.2 min and nine in group B with a mean duration of 2.8 min) or in the requirement for ephedrine (four in group A and

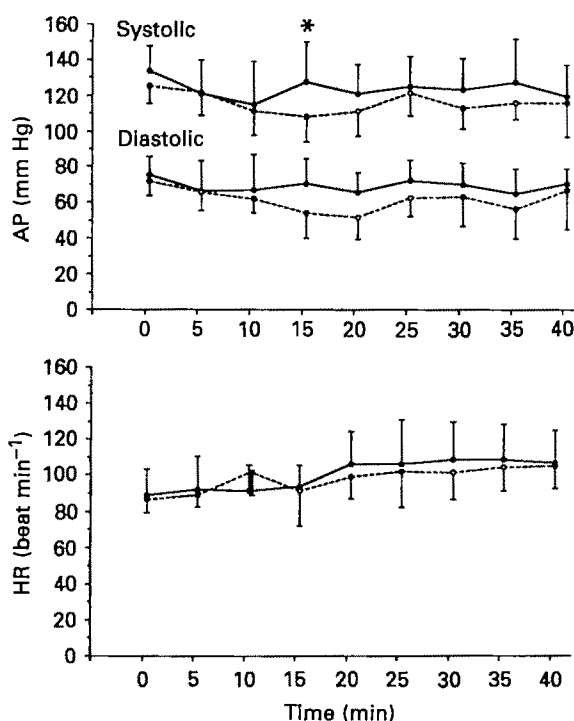


FIG. 2. Maternal heart rate (HR) and arterial pressure (AP) during extradural anaesthesia (mean, SD). Time 0 min is immediately before first dose of local anaesthetic. — = 2% Lignocaine; --- = 2% lignocaine + adrenaline. * $P < 0.05$.

five in group B). There was no significant difference in the maternal heart rates between the two groups.

Feto-placental unit

Extradural anaesthesia (with or without the adrenaline-containing solution) did not signifi-

cantly alter the A:B ratio, corrected A:B ratio, PI or FHR (table IV). There was no difference in umbilical arterial pH or Apgar scores between the two groups. A:B ratios, PI and FHR were not altered significantly during episodes of hypotension or after treatment with ephedrine (table V). The umbilical arterial pH and Apgar scores of neonates from mothers who had had hypotensive episodes were not significantly different from those of neonates from mothers who had remained normotensive throughout the procedure (table VI).

Complications

Transient symptoms suggestive of lignocaine toxicity (nasal paraesthesiae) occurred in one patient in group A at a plasma concentration of lignocaine $2.09 \mu\text{g ml}^{-1}$. One patient in group B experienced pain when the uterus was exteriorized after delivery and required general anaesthesia to complete surgery.

DISCUSSION

The principal effects of adrenaline in local anaesthetic solutions are to reduce local blood flow, limit systemic absorption of local anaesthetic and enhance neuronal uptake [4, 12], resulting in an increased depth of analgesia for a given dose [2]. We were not surprised to find, therefore, that the mean dose of lignocaine required to produce a satisfactory block for Caesarean section was significantly smaller in those who had received the adrenaline-containing solution. The potential for maternal lignocaine toxicity is high in Caesarean section because large doses are used over a short

TABLE IV. Feto-placental unit. FHR = fetal heart rate; U = uncorrected for FHR; C = corrected for FHR. Mean values (SD). No significant differences between groups

		A:B ratio		Pulsatility index		FHR (beat min ⁻¹)		Umbilical arterial pH	No. of patients with Apgar scores < 8	
		Before extradural	Before surgery	Before extradural	Before surgery	Before extradural	Before surgery		1 min	5 min
2% Lignocaine	U	2.15	2.30	0.89	0.89	143.5	136.2	7.26	1	0
	(n = 10)	(0.39)	(0.50)	(0.20)	(0.17)	(9.23)	(19.39)	(0.18)		
	C	2.19	2.26							
		(0.27)	(0.54)							
2% Lignocaine + adrenaline	U	2.11	2.20	0.82	0.82	141.1	140.9	7.28	0	0
	(n = 9)	(0.25)	(0.29)	(0.12)	(0.12)	(11.39)	(11.96)	(0.10)		
	C	2.12	2.11							
		(0.18)	(0.16)							

TABLE V. Effect of hypotension and ephedrine on A:B ratio, pulsatility index and fetal heart rate (FHR) (mean (SD)). U = Uncorrected for FHR; C = corrected for FHR. No significant differences between groups

	Before extradural (n = 20)	Hypotension (n = 15)	After ephedrine (n = 9)	Before surgery (n = 19)
A:B ratio				
U	2.08 (0.32)	2.22 (0.24)	2.15 (0.21)	2.14 (0.32)
C	2.09 (0.21)	2.07 (0.25)	2.00 (0.21)	2.07 (0.22)
Pulsatility index	0.91 (0.16)	0.94 (0.13)	0.89 (0.08)	0.82 (0.14)
FHR (beat min ⁻¹)	141.5 (10.44)	132.9 (12.80)	129.2 (17.49)	138.1 (14.20)

TABLE VI. Comparison of fetal outcome where mothers have been hypotensive with that where mothers have been entirely normotensive (mean (SD)). No significant differences between groups

	Umbilical arterial pH	No. of patients with Apgar scores < 8	
		1 min	5 min
Normotensive (n = 4)	7.29 (0.29)	0	0
Hypotensive (n = 15)	7.24 (0.07)	1	0

time interval. Placental transfer of lignocaine also occurs readily and one (unconfirmed) report has described neonatal hypotonicity as a consequence [13]. It was important, therefore, to find that both maternal and neonatal plasma concentrations of lignocaine were reduced significantly when the adrenaline-containing solution was used. The fact that this was caused by reduced systemic absorption rather than merely the smaller doses used in the adrenaline group was reflected in the lower plasma concentration:dose ratios. Lignocaine toxicity in adults may begin to occur at plasma concentrations of 5 µg ml⁻¹ and is manifest usually by central nervous system disturbance [14]. Plasma concentrations in this study were all considerably smaller than this value, including those in the patient who experienced nasal paraesthesia.

The enhanced neuronal uptake afforded by adrenaline might have been expected also to produce the more rapid onset of block which Bromage and colleagues have shown with 2% lignocaine and Murphy and colleagues have shown with etidocaine [4, 5]. However, this effect has not been confirmed by all investigators and

Abboud and colleagues have demonstrated a slowing of the onset of anaesthesia when adrenaline was used with 2% lignocaine [15]. Although the difference did not reach statistical significance in our study, there was a trend towards faster onset of block when the adrenaline solution was used.

One concern with the use of 2% lignocaine for Caesarean section is whether or not the duration of action is long enough to provide consistently complete analgesia throughout the operation. It is our experience that, if the block is adequate before the start of surgery, 2% lignocaine provides anaesthesia for the duration. In this study, the failure of anaesthesia which necessitated intrathecal block was almost certainly caused by incorrect placement of the extradural catheter and that which necessitated general anaesthesia was a result of a combination of prolonged surgery with exteriorization of uterus.

The addition of adrenaline to lignocaine for extradural analgesia in labour has been shown to prolong the duration of useful analgesia [6]. To determine if this was true also of the analgesia provided by extradural block in Caesarean section, we documented the time at which further analgesia was required. Again, although it appeared from the mean values that those who received the plain solution required analgesia earlier, the wide range of values within each group suggested that the difference from the adrenaline group was not significant. The trend towards a faster onset and longer duration of block in the adrenaline group was, however, in keeping with the distinct clinical impression that the dose was easier to titrate and the block more reliable when adrenaline was used.

Several studies have examined the effect of adrenaline-containing extradural solutions on

maternal cardiovascular variables, but results have differed. Abboud and his co-workers have found that, while the addition of adrenaline to bupivacaine produced less hypotension, the incidence of hypotension was not affected when adrenaline was used with lignocaine solution [6, 15, 16]. Conversely, Bonica and colleagues showed that lignocaine and adrenaline solutions produced more hypotension (and faster heart rates) than plain lignocaine solutions [17]. These investigators believe that the haemodynamic differences may be attributed to the systemic beta-adrenergic effect of absorbed adrenaline. The cardiovascular changes caused by the adrenaline-containing solution in our study were similar to the findings of Bonica with smaller arterial pressures and an early (although not statistically significant) increase in heart rate. Beta-adrenergic stimulation might account fully for these differences as well, but a contributory factor could also have been the trend of the adrenaline group to have a faster onset of block and, therefore, more rapid peripheral vasodilatation.

There has been uncertainty regarding the effect of systemically absorbed adrenaline on the foeto-placental circulation [18–21]. In this study the influence of anaesthetic technique on umbilical blood flow was assessed by measuring indices of placental resistance. This has been used successfully to predict acute and chronic fetal compromise [7, 22, 23]. It was important to find, therefore, that not only was the placental flow resistance unaltered by extradural anaesthesia itself, but also it was unaffected by the use of the adrenaline-containing solution. Adequacy of umbilical blood flow was supported by the fact that fetal outcome (in terms of umbilical arterial pH and Apgar scores) was the same whether adrenaline was used or not. In addition, neither the short-lived episodes of hypotension nor the ephedrine used for treatment had an adverse effect on umbilical blood flow or fetal outcome. Although this could have been the result of prompt detection and treatment, there is evidence that an autoregulatory mechanism exists within the umbilical circulation which may compensate for brief changes in maternal pressure [24].

We conclude that, while 2% lignocaine may provide satisfactory extradural anaesthesia for elective Caesarean section, addition of adrenaline 1:200 000 to the solution has several advantages: it reduces dose requirements, plasma concentra-

tions of lignocaine and, probably, the time to onset of satisfactory block, without adverse effects on mother or fetus.

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REFERENCES

1. Reid JA, Thorburn J. Extradural bupivacaine or lignocaine anaesthesia for elective Caesarean section: the role of maternal posture. *British Journal of Anaesthesia* 1988; 61: 149–153.
2. Covino BG. General considerations, toxicity and complications of local anaesthesia. In: Nimmo WS, Smith G, eds. *Anaesthesia*. Oxford: Blackwell, 1989; 1011–1033.
3. Marx GF. Cardiotoxicity of local anaesthetics—the plot thickens. *Anesthesiology* 1984; 60: 3–5.
4. Bromage PR, Burfoot MF, Crowell DE, Pettigrew RT. Quality of epidural blockade. 1: Influence of physical factors. *British Journal of Anaesthesia* 1964; 36: 342–352.
5. Murphy TM, Mather LE, Stanton-Hicks Md'A, Bonica JJ, Tucker GT. The effects of adding adrenaline to etidocaine and lignocaine in extradural anaesthesia. 1: block characteristics and cardiovascular effects. *British Journal of Anaesthesia* 1976; 48: 893–897.
6. Abboud TK, David S, Nagappala S, Costandi J, Yanagi T, Haroutunian S, Yeh SU. Maternal, fetal, and neonatal effects of lidocaine with and without epinephrine for epidural anesthesia in obstetrics. *Anesthesia and Analgesia* 1984; 63: 973–979.
7. Trudinger BJ, Giles WB, Cook CM, Bombardieri J, Collins L. Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. *British Journal of Obstetrics and Gynaecology* 1985; 92: 23–30.
8. Gosling RG, King DH. Ultrasonic angiography. In: Marcus AW, Adamson L, eds. *Arteries and Veins*, 1st Edn. Edinburgh: Longman, 1975; 61–98.
9. Mires G, Dempster J, Patel NB, Crawford JW. The effect of fetal heart rate on umbilical artery flow velocity waveforms. *British Journal of Obstetrics and Gynaecology* 1987; 94: 665–669.
10. Mansouri H, Gagnon R, Hunse C. Relationship between fetal heart rate and umbilical blood flow velocity in term human fetuses during labor. *American Journal of Obstetrics and Gynecology* 1989; 160: 1007–1012.
11. Howard PJ, Moore J. The estimation of lignocaine concentrations in plasma by HPLC. *Chromatography and Analysis* 1990; Feb: 9–10.
12. Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetics. *Clinical Pharmacokinetics* 1979; 4: 241–278.
13. Scanlon JW, Brown WU jr, Weiss JB, Alper MH. Neurobehavioral responses of newborn infants after maternal epidural anesthesia. *Anesthesiology* 1974; 40: 121–128.
14. Folds FF, Molloy R, McNall PG, Koukal LR. Comparison of toxicity of intravenously given local anesthetic agents in man. *Journal of the American Medical Association* 1960; 172: 1493–1498.

15. Abboud TK, Kim KC, Noueihed R, Kuhnert BR, DerMardirossian N, Moumdjian J, Sarkis F, Nagappala S. Epidural bupivacaine, chloroprocaine or lidocaine for Cesarean section—maternal and neonatal effects. *Anesthesia and Analgesia* 1983; 62: 914–919.
16. Abboud TK, Shiek-ol-Eslam A, Yanagi T, Murakawa K, Costandi J, Zakarian M, Hoffman D, Haroutunian S. Safety and efficacy of epinephrine added to bupivacaine for lumbar epidural analgesia in obstetrics. *Anesthesia and Analgesia* 1985; 64: 585–591.
17. Bonica JJ, Akamatsu TJ, Berges PU, Morikawa K, Kennedy WF. Circulatory effects of peridural block. *Anesthesiology* 1971; 34: 514–522.
18. Rosenfeld CR, Barton MD, Meschia G. Effects of epinephrine on distribution of blood flow in the pregnant ewe. *American Journal of Obstetrics and Gynecology* 1976; 124: 156–163.
19. deRosayro AM, Nahrwold ML, Hill AB. Cardiovascular effect of epidural epinephrine in the pregnant sheep. *Regional Anesthesia* 1981; 6: 4–7.
20. Jouppila R, Jouppila P, Kuikka J, Hollmén A. Placental blood flow during Cesarean section under lumbar extradural analgesia. *British Journal of Anaesthesia* 1978; 50: 275–278.
21. Albright GA, Jouppila R, Hollmén AI, Jouppila P, Vierola H, Koivula A. Epinephrine does not alter human inatervillous blood flow during epidural anesthesia. *Anesthesiology* 1981; 54: 131–135.
22. Lingman G, Laurin J, Marsàl K. Circulatory changes in fetuses with imminent asphyxia. *Biology of the Neonate* 1986; 49: 66–73.
23. Trudinger BJ, Cook CM, Jones L, Giles WB. A comparison of fetal heart rate monitoring and umbilical artery waveforms in the recognition of fetal compromise. *British Journal of Obstetrics and Gynaecology* 1986; 93: 171–175.
24. Kingdom JCP, Ryan G, Whittle MJ, Doyle J, Connell JMC. Atrial natriuretic peptide: a regulator of the fetoplacental circulation? *American Journal of Obstetrics and Gynecology* 1991; 164: 242.

USE OF A 25-GAUGE WHITACRE NEEDLE TO REDUCE THE INCIDENCE OF POSTDURAL PUNCTURE HEADACHE

J. LYNCH, I. KRINGS-ERNST, K. STRICK, K. TOPALIDIS, H. SCHAAF AND M. FIEBIG

SUMMARY

We studied 200 orthopaedic inpatients (111 males) aged 15-84 yr who received spinal anaesthesia with one of two types of Whitacre spinal needle: 22-gauge or 25-gauge. The incidence of headache, backache, failure of spinal anaesthesia and patient acceptability was investigated using a questionnaire. The incidence of postdural puncture headache (PDPH) was 4% in the 22-gauge group and 2% in the 25-gauge group. The incidence of backache and headache of other origin was similar in both groups. Spinal anaesthesia was carried out successfully in all patients in both groups. Patient acceptance was high (98%) and there were no serious complications observed. We conclude that spinal anaesthesia is easy to perform with a 25-gauge pencil-point needle and is associated with a low incidence of PDPH.

KEY WORDS

Anaesthetic techniques: regional, spinal. Complications: headache. Equipment: Whitacre spinal needle (25-gauge).

The occurrence of postdural puncture headache (PDPH) after spinal anaesthesia limits wider use of this useful method of anaesthesia [1]. While the size of the needle is important in the aetiology of PDPH, the configuration of the needle tip has received increasing attention in recent years [2] and has led to revival of interest in the Whitacre needle. This has been supported by reports of a low incidence of PDPH in clinical studies using Whitacre spinal needles [3, 4]. Recently a 25-gauge version has become available. It is thought that a smaller pencil-point needle may possess the low incidence of PDPH associated with extreme fine gauge Quincke needles (e.g. 29-gauge) while retaining the ease of handling of the larger 22-

gauge Whitacre needle [5]. In a controlled study of 200 orthopaedic patients, we have compared the 25-gauge needle with the 22-gauge Whitacre needle for incidence of PDPH, backache, failure to achieve spinal anaesthesia and patient acceptance.

PATIENTS AND METHODS

After obtaining informed consent and approval from the hospital Ethics Committee, we studied 200 inpatients (ASA I-III) aged 15-84 yr undergoing elective orthopaedic procedures. Patients were allocated randomly to receive spinal anaesthesia with either a 22-gauge Whitacre (Becton and Dickinson (BD) o.d. 0.7 mm) or a 25-gauge Whitacre needle (BD, o.d. 0.5 mm).

Premedication consisted of flunitrazepam 0.03 mg kg⁻¹ orally 1-2 h before induction of anaesthesia. Spinal anaesthesia was performed using a midline approach at the L3-4 interspace in the lateral position for most patients using one of the above spinal needles. The sitting position was adopted or the L2-3 interspace was used for spinal puncture when indicated clinically. A 20-gauge introducer (Braun, Germany) was used at the discretion of the individual anaesthetist. Subcutaneous infiltration with 1% mepivacaine was performed with a short 27-gauge needle to facilitate spinal puncture. Hyperbaric 0.5% bupivacaine 2-4 ml or hyperbaric 5% lignocaine 1-2 ml was used throughout and the orifice of the

This article is accompanied by Editorial II.

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TABLE I. Patient characteristics (mean (SD) [range]) from two groups of patients receiving spinal anaesthesia with a 22- or a 25-gauge Whitacre needle

	Group I Whitacre 25-gauge (n = 100)	Group II Whitacre 22-gauge (n = 100)
Sex (M/F)	59/41	52/48
Age (yr)	38 (22) [16-84]	39 (17) [15-84]
Height (cm)	173 (12) [152-198]	173 (8.6) [150-193]
Weight (kg)	73 (15) [48-105]	73 (14) [53-100]

TABLE II. Complications of spinal anaesthesia in the 25-gauge and 22-gauge groups. No significant differences between groups

	25-gauge (n = 100)	22-gauge (n = 100)
PDPH	2 (2%)	4 (4%)
Atypical headache	5 (5%)	3 (3%)
Backache	9 (9%)	9 (9%)

Whitacre needle was always directed cephalad. After injection, the patient was immediately placed supine. Monitoring consisted of continuous ECG recording, measurement of arterial pressure every 5 min and pulse oximetry (Nellcor N-1000). The patient was allowed to ambulate 6-48 h after operation, depending on the type of surgery performed. All patients were seen on the day of surgery and at 3-5 days after operation, when they were questioned by one of the authors using a standard questionnaire, or contacted by telephone if discharged earlier. The patients were questioned for headache, its severity, localization, character (e.g. posture-dependent), duration, the presence or absence of associated symptoms and their assessment of the procedure. The headache was considered to be of the classical postdural puncture type [1] if it fulfilled the following

conditions: aggravated by the erect or sitting position, relief on lying flat, mainly occipital or frontal with aggravation on coughing, sneezing or straining. Student's *t* test for independent variables or, where appropriate, chi-square test was used to examine statistical significance; *P* < 0.05 was considered significant.

RESULTS

Data from 200 patients (111 men and 89 women) were evaluated. The groups were similar in respect of age, height and body weight (table I). Successful dural puncture was achieved in all patients in both groups. The overall incidence of classical PDPH was 2% in the 25-gauge and 4% in the 22-gauge group, and the incidence of non-spinal headache and backache was similar in both groups (table II). The mean duration of headache was 44 h (range 24-64 h) and 57.5 h (range 8-80 h) in the 25-gauge and 22-gauge groups, respectively. Clinical features of the patients with PDPH are shown in table III. All patients suffering from PDPH had received bupivacaine intrathecally and in no patient were more than two attempts at lumbar puncture necessary. The headache responded to bed rest and analgesics in all patients and in none did the severity or duration of the headache warrant extradural blood patching. Patient acceptance of spinal anaesthesia was high and similar in both groups (98%).

DISCUSSION

Spinal anaesthesia is a popular anaesthetic technique, with a low complication rate, but it carries the special risk of postdural puncture headache [1]. Many factors have been mentioned as influencing the incidence of PDPH, but the most important is needle size [1, 6].

TABLE III. Clinical features of patients with PDPH. (Dural puncture achieved at first attempt in each patient)

Age (yr)	Sex	Needle gauge	Appearance of symptoms (postop. day)	Severity	Duration (h)
44	F	25	1	Slight	24
38	F	25	1	Slight	64
61	F	22	1	Moderate	72
24	F	22	1	Severe	80
16	M	22	1	Slight	72
20	F	22	2	Slight	8

The influence of the configuration of the needle tip on the incidence of PDPH has recently been the subject of renewed interest [7], although first reports of the use of 20-gauge pencil-point needles date back 40 years [8, 9]. In spite of these early encouraging results, the Whitacre needle failed to find widespread use, and more recent studies reported an incidence of 11% and 14% for PDPH using a 22-gauge Whitacre needle [10, 11]. Pencil-point needles have a theoretical advantage in reducing trauma to the dural fibres [12] and recent experimental studies suggest that the dural defect produced by 22-gauge Whitacre pencil-point needles is smaller [13] and leads to a smaller loss of CSF than with comparable Quincke needles [12, 14, 15]. Clinical studies demonstrating an incidence of PDPH of less than 4% in younger patients using a Whitacre 22-gauge needle [3, 4] support these experimental findings and are in keeping with our results using the 22-gauge needle.

Based on these observations, it seemed reasonable, therefore, to expect that a smaller Whitacre needle would cause a similar reduction in CSF loss after dural puncture in comparison with an equivalent size Quincke needle. This was not investigated in the present study, but recent clinical studies have shown that the use of 25- and 26-gauge needles have failed to reduce consistently the rate of PDPH, especially in younger patients [6, 11, 16–22]. Flaaten and Raeder [20] have reported an incidence of 37.2% for PDPH using 25-gauge needles. In the light of these findings, a 2% incidence of PDPH with the 25-gauge Whitacre needle is clearly superior to that reported with 25- or 26-gauge Quincke needles and approaches results obtained with 29-gauge needles. As in other studies [16, 17], we found that PDPH affected mainly young females (5.6% *vs* 0.9%), as four of five females suffering from PDPH were younger than 45 yr. The incidence of PDPH for females was less in the 25-gauge group (4.9% *vs* 6.2%). This low incidence of PDPH is even more impressive if the results in patients younger than 40 yr are analysed, where a fourfold greater incidence of PDPH was observed in the 22-gauge group compared with the 25-gauge group (5.3% *vs* 1.4%). Dittmann and Renkl found a similar incidence of PDPH (1.37%) using a 29-gauge needle in a large group of patients [23].

The use of extremely fine-gauge needles is thought to markedly reduce the incidence of PDPH [24]; however, their use is associated with

a higher failure rate of spinal anaesthesia than following the use of larger needles [25, 26], reaching 25% in some cases [27]. The use of an introducer is also necessary and, if used incautiously, this may cause inadvertent dural puncture [25]. Moreover, there are reports of severe PDPH requiring blood patching after use of 29-gauge needles in obstetric patients [28]. These needles are also expensive and they should not be reused [29]. A further theoretical advantage of the 25-gauge Whitacre needle compared with the 22-gauge Whitacre needle and 29-gauge needles with a Quincke tip, is the provision of a transparent hub making earlier identification of CSF possible [7].

Although the use of a Whitacre needle feels different from that of a Quincke needle [2], expertise is attained quickly as testified by the low rate of attempts at spinal anaesthesia in this study. The Whitacre 25-gauge needle is still rigid enough to be used without an introducer, although this may be useful initially for those inexperienced in the use of Whitacre needles.

The incidence of backache was similar in both groups, although clearly less than in other reports, possibly because of infiltration with local anaesthetic before spinal anaesthesia was performed [20, 25]. Lack of occurrence of inability to perform spinal anaesthesia in both groups was possibly because of the predominantly young patients studied and the ease of use of the Whitacre needle, even in inexperienced hands [30].

Further methods proposed to reduce the incidence of PDPH include the use of the paramedian approach with an acute angle of needle insertion and the use of conical-tipped spinal needles [14]. Of these, the Sprotte needle seems to be the most promising and is claimed to be devoid of the disadvantages of the original Whitacre needle [31]. However, recent studies reported an incidence of PDPH of 0–8.6% [32, 33] and further investigations are necessary to clarify this question. We conclude that spinal anaesthesia is easy to perform with a Whitacre 25-gauge needle and is associated with a low incidence of PDPH.

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REFERENCES

- Gerard KW, Fagraeus L. Postspinal headache. *Seminars in Anesthesiology* 1990; 9: 68-74.
- Thomas TA, Noble HA. A re-evaluation of the Whitacre spinal needle in obstetric anaesthesia—a pilot study. *Anaesthesia* 1990; 45: 489.
- Kreuscher H, Sandmann G. Relief of headache following spinal anesthesia by use of Whitacre cannula. Clinical study. (In German.) *Regional Anaesthesia* 1989; 12: 46-49.
- Sami HM, Skaredorf MN. In-hospital incidence of post-lumbar puncture headache in Caesarean section patients associated with the 22G Whitacre needle. *Regional Anaesthesia* 1989; 14: 44.
- Carrie LE. Whitacre and pencil-point spinal needles: some points to consider. *Anaesthesia* 1990; 45: 1097-1098.
- Sarma VJ, Boström U. Intrathecal anaesthesia for day-care surgery. A retrospective study of 160 cases using 25- and 26-gauge spinal needles. *Anaesthesia* 1990; 45: 769-771.
- Carrie LES, Collins PD. 29-gauge spinal needles. *British Journal of Anaesthesia* 1991; 66: 145-146.
- Hart JR, Whitacre RJ. Pencil-point needle in prevention of postspinal headache. *Journal of the American Medical Association* 1951; 147: 657-658.
- Haraldson S. Headache after spinal anesthesia: experiments with a new spinal needle. *Anesthesiology* 1951; 12: 321-327.
- Eckstein KL, Rogacev Z, Vincente-Eckstein A, Grahovac Z. Prospective comparative study of post-spinal headaches in young patients (< 51 years). (in German.) *Regional Anaesthesia* 1982; 5: 57-61.
- Martin YN, Guivarc'h M, Olivier J, Ducrot P. Rôle du calibre 22G et 25G de l'aiguille dans l'apparition des céphalées après rachianesthésie. *Cahiers d'Anesthésiologie* 1987; 35: 535-537.
- Cruikshank RH, Hopkinson JM. Fluid flow through dural puncture sites. An *in vitro* comparison of needle point types. *Anaesthesia* 1989; 44: 415-418.
- Dittmann H, Schäfer HG, Ulrich J, Bond-Taylor W. Anatomical reevaluation of lumbar dura mater with regard to postspinal headache. Effect of dural puncture. *Anaesthesia* 1988; 43: 635-637.
- Ready LB, Cuplin S, Haschke RH, Nessly M. Spinal needle determinants of rate of transdural fluid leak. *Anesthesia and Analgesia* 1989; 69: 457-460.
- Sami HM, McNulty JA, Skaredorf MN, Fox LM. The effect of spinal needle shape and bevel orientation on the size and shape of the dural defect: An SEM study in dogs. *Anesthesiology* 1989; 71: A674.
- Flaaten H, Rodt S, Rosland J, Vamnes J. Postoperative headache in young patients after spinal anaesthesia. *Anaesthesia* 1987; 42: 202-205.
- Rasmussen BS, Blom L, Hansen P, Mikkelsen SS. Postspinal headache in young and elderly patients. Two randomised, double-blind studies that compare 20- and 25-gauge needles. *Anaesthesia* 1989; 44: 571-573.
- Barker P. Headache after dural puncture. *Anaesthesia* 1989; 44: 696-697.
- Neal JM, Bridenbaugh MD, Mulroy MF, Palmen BD. Incidence of post dural puncture headache is similar between 22G Greene and 26G Quincke spinal needles. *Anesthesiology* 1989; 71: A678.
- Flaaten H, Raeder J. Spinal anaesthesia for outpatient surgery. *Anaesthesia* 1985; 40: 1108-1111.
- Thornberry EA, Thomas TA. Posture and post-spinal headache. A controlled trial in 80 obstetric patients. *British Journal of Anaesthesia* 1988; 60: 195-197.
- Flaaten H, Rodt SA, Vamnes J, Rosland J, Wisborg T, Koller ME. Postdural puncture headache. A comparison between 26- and 29-gauge needles in young patients. *Anaesthesia* 1989; 44: 147-149.
- Dittmann M, Renkl F. Spinal anesthesia with extremely fine needles. *Anesthesiology* 1989; 70: 1035-1036.
- Weeks S. Spinal headache—prevention and treatment. *Canadian Journal of Anaesthesia* 1990; 37: 4/Sliit-Slviii.
- Dahl JB, Schultz P, Anker-Moller E, Christensen EF, Staunstrup HG, Carlsson P. Spinal anaesthesia in young patients using a 29-gauge needle: technical considerations and an evaluation of postoperative complaints compared with general anaesthesia. *British Journal of Anaesthesia* 1990; 64: 178-182.
- Lybecker H, Moller JT, May O, Nielsen HK. Incidence and prediction of postdural puncture headache. A prospective study of 1021 spinal anesthetics. *Anesthesia and Analgesia* 1990; 70: 389-394.
- Lesser P, Bembridge M, Lyons G, MacDonald R. An evaluation of a 30-gauge spinal needle for spinal anaesthesia for Caesarean section. *Anaesthesia* 1990; 45: 767-768.
- Fitzgibbon D, Gardiner J. Postdural puncture headache with 29-gauge spinal needles. *Anaesthesia* 1990; 45: 593.
- Tuominen MK, Keskinen K, Rosenberg PH. Scanning electron microscope examination of resterilized 29-gauge spinal needles. *Anesthesiology* 1988; 69: 123-125.
- Bridenbaugh PO, Greene NM. Spinal neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade*. Philadelphia: JB Lippincott, 1988; 238.
- Sprotte G, Schedel R, Pajunk H, Pajunk H. Eine atraumatische Universalkanüle fuer einzeitige Regionalanästhesien. *Regional Anaesthesia* 1987; 10: 104-108.
- Büttner J, Wresch KP, Klose R. Does a conical spinal needle offer advantages over the conventional type? (in German.) *Regional Anaesthesia* 1990; 13: 124-128.
- Cesarini M, Torielli R, Lahaye F, Mene JH, Cabirol C. Sprotte needle for intrathecal anaesthesia for Caesarean section: incidence of postdural puncture headache. *Anaesthesia* 1990; 45: 656-658.

EFFECT OF I.V. LOW-DOSE ADRENALINE AND PHENYLEPHRINE INFUSIONS ON PLASMA CONCENTRATIONS OF BUPIVACAINE AFTER LUMBAR EXTRADURAL ANAESTHESIA IN ELDERLY PATIENTS†

N. E. SHARROCK, G. GO AND R. MINEO

SUMMARY

Thirty patients undergoing primary total hip replacement under lumbar extradural anaesthesia with 0.75% bupivacaine 25 ml were allocated randomly to receive either low-dose adrenaline or phenylephrine infusions i.v. throughout surgery. Haemodynamic measurements and arterial blood samples were obtained before the extradural injection and at 10, 20, 30, 40, 50, 60 and 90 min thereafter. Peak arterial plasma concentrations of bupivacaine were observed 10 min after extradural anaesthesia and were significantly lower in patients receiving adrenaline infusions. Cardiac output was significantly greater in patients receiving adrenaline infusions ($P < 0.01$). It is postulated that the smaller circulating concentrations of bupivacaine observed in patients receiving adrenaline were caused by increased cardiac output and a greater volume of distribution than in patients receiving phenylephrine.

KEY WORDS

Anaesthetic techniques: extradural. Anaesthetics, local: bupivacaine. Heart: cardiac output.

Pharmacokinetic studies have demonstrated increased plasma concentrations of lignocaine after i.v. infusions of lignocaine in low flow states [1-3]. Increased plasma concentrations of local anaesthetic may contribute to circulatory depression by either myocardial or peripheral vascular effects [4]. Cardiac output may decrease after extradural anaesthesia, particularly in elderly patients who develop hypotension [5, 6]. It is important, therefore, to know the influence of low cardiac output

states on the peak circulating concentrations of local anaesthetic, as this may contribute to further circulatory depression.

Adrenaline and phenylephrine are often used to maintain arterial pressure after extradural anaesthesia and are known to have different circulatory effects [7]. Adrenaline increases cardiac output secondary to its inotropic action [7-9], whereas phenylephrine is associated with a reduction in cardiac output [7]. We have compared these agents as a means of assessing the influence of cardiac output on peak local anaesthetic concentrations after extradural anaesthesia.

PATIENTS AND METHODS

After Institutional Review Board approval, 30 patients undergoing total hip replacement under lumbar extradural anaesthesia were allocated randomly to receive i.v. infusions of either low-dose adrenaline or phenylephrine to maintain mean arterial pressure at 50-60 mm Hg throughout surgery.

Patients received no premedication until arrival in the operating room, where they were sedated with midazolam 1-3 mg and fentanyl 25-50 µg i.v. Patients received Ringer's lactate 70 ml h⁻¹ overnight, but were not fluid loaded before the extradural anaesthetic. A 20-gauge radial artery

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TABLE I. Patient data, intraoperative fluid requirements and dose of vasopressors (mean (range or SD)) in patients in whom plasma bupivacaine concentrations were measured ($n = 30$). No significant differences between groups

	Adrenaline ($n = 15$)	Phenylephrine ($n = 15$)
Sex (M/F)	3/12	3/12
Age (yr)	69.9 (57–85)	71.6 (63–77)
Ht (cm)	166.8 (8.0)	161.9 (7.5)
Wt (kg)	78.3 (19.9)	71.8 (13.3)
Intra-op. fluid (ml)	1225.0 (352)	1132.0 (270.0)
Dose ($\mu\text{g min}^{-1}$)	2.6 (1.02)	10.6 (6.2)

cannula was inserted percutaneously. In the first 15 patients studied, thermodilution pulmonary artery catheters were inserted via the right internal jugular vein.

All extradural anaesthetics were performed with the patient in the lateral position and the operative side uppermost. Injections were performed at the L1–2 interspace as follows: 0.75 % bupivacaine 5 ml was infiltrated in the paravertebral muscle and a 17-gauge Tuohy needle passed into the extradural space at L1–2 using the paramedian approach. Plain 0.75 % bupivacaine 25 ml was injected via the 17-gauge Tuohy needle in 5-ml aliquots with 15 s between each 5-ml injectate. This resulted in a sensory level to pinprick of T4 or above.

In the first 15 patients, serial haemodynamic measurements were made with the subject in the lateral decubitus position before the extradural injection and at 10, 20, 30, 40, 50, 60 and 90 min thereafter. Heart rate, mean arterial and pulmonary artery pressures were recorded. Cardiac outputs were measured in triplicate using a thermodilution technique (Spectramed) by injecting 10 ml of saline at room temperature. The shape of the temperature decay curves was assessed and the mean of the two best curves was used. In all patients, mean arterial pressure decreased to between 50 and 60 mm Hg and was maintained within this range throughout surgery, to minimize intraoperative blood loss and facilitate surgical conditions.

Interim analysis was performed after the first 15 patients, resulting in a modification of the procedure for the subsequent 15 patients, in whom thermodilution cardiac output was not measured.

Blood samples were drawn from the arterial line before the extradural injection and at 10, 20, 30,

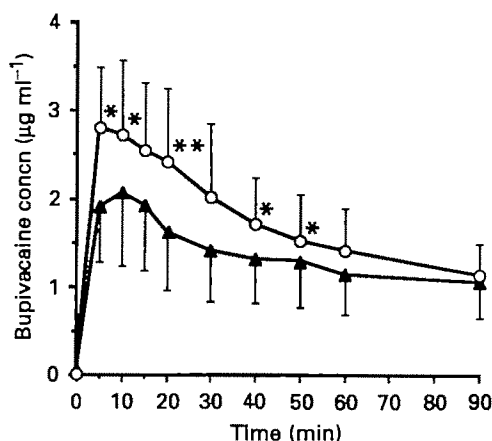


FIG. 1. Arterial plasma concentrations of bupivacaine after extradural injection of 0.75 % bupivacaine plain 25 ml in 15 patients receiving low-dose adrenaline ($\blacktriangle$) and 15 receiving phenylephrine ($\circ$) i.v. infusions (mean, SD). * $P < 0.05$; ** $P < 0.01$.

40, 50, 60 and 90 min thereafter. Samples were obtained also at 5 and 15 min after extradural injection in the last 15 of the 30 patients, to define the time to peak blood concentration. All blood samples were collected in heparinized tubes and centrifuged immediately at 4 °C. Plasma samples were stored at -70 °C until required for assay.

Measurement of plasma bupivacaine concentration was by capillary gas chromatography with nitrogen selective detection (performed at the National Medical Services, Inc. Willow Grove, PA 19090, U.S.A.) The limit of quantitation was 0.02 $\mu\text{g ml}^{-1}$ and inter-assay coefficient of variation at 0.1 $\mu\text{g ml}^{-1}$ was 7.5 %.

Analysis

Differences in plasma bupivacaine concentrations and cardiac outputs were assessed by one-way analysis of variance (ANOVA) for repeated measures and the Scheffé F test. Differences in patient data and intraoperative fluid between groups were assessed using Student's t test. The relationship between cardiac output and arterial plasma concentration of bupivacaine was assessed using simple linear regression analysis. Significance was accepted at the 0.05 level.

RESULTS

There were no significant differences between patient groups regarding patient data or i.v. fluid administered during operation (table I). The arterial plasma concentrations of bupivacaine after

TABLE II. Patient data and intraoperative fluid requirements (mean (range or SD)) in patients in whom serial cardiac outputs were measured ($n = 15$). No significant differences between groups

	Adrenaline ($n = 6$)	Phenylephrine ($n = 9$)
Sex (M/F)	1/5	1/8
Age (yr)	77.0 (67–85)	71.9 (68–77)
Ht (cm)	163.0 (8.5)	161.8 (8.7)
Wt (kg)	79.9 (25.8)	68.4 (15.4)
Intra-op. fluid (ml)	1237.5 (103)	1077.8 (98.3)

extradural anaesthesia in patients who received either i.v. infusions of low-dose adrenaline or phenylephrine are shown in figure 1. Significantly smaller arterial values of bupivacaine were observed in patients receiving adrenaline at 5, 10, 20, 30 and 40 min after injection. Peak local anaesthetic concentrations occurred 5 min after extradural injection with phenylephrine, whereas the peak value did not occur until 10 min after extradural injection in patients receiving low-dose adrenaline infusions. By 20 min the arterial concentrations of bupivacaine had declined significantly from their respective peak values in both groups ($P < 0.0001$).

Cardiac output, heart rate, mean arterial pressure and pulmonary artery diastolic pressure of the initial 15 patients (table II) receiving adrenaline or phenylephrine are shown in figure 2. There was a significantly greater cardiac output at all times in patients receiving adrenaline. Similar responses in heart rate and mean arterial pressure were observed in the remaining 15 patients receiving either adrenaline or phenylephrine.

The peak circulating concentrations of local anaesthetic showed only a weak correlation with cardiac output 10 min after extradural injection ($r = 0.39$).

DISCUSSION

We have demonstrated that peak arterial concentrations of bupivacaine were evident within 10 min of extradural injection and were significantly greater in patients who received phenylephrine than those who received low-dose adrenaline infusions. In previous studies, peak concentrations were shown to occur 15–30 min after extradural anaesthesia when blood was sampled from the antecubital vein [10, 11]. Our observations suggest that toxic reactions to injection of local anaesthetic are more likely to occur

within 5–10 min after extradural injection rather than later. Although relatively large doses of bupivacaine were used and peak arterial concentrations exceeded $4 \mu\text{g ml}^{-1}$ in several patients who received phenylephrine, no toxic reactions were noted. However, it is possible that these high values might contribute to additional circulatory depression immediately after extradural anaesthesia, particularly in patients with heart failure or low cardiac output.

Cardiac output was measured only in the first 15 patients as a significant haemodynamic difference between agents was already apparent. Furthermore, the haemodynamic effects of extradural anaesthesia with or without inotropic support have been reported previously [5–7, 12]. Thereafter, we were more interested in obtaining a large number of patients to define the timing of the peak concentrations of local anaesthetic, which occurred as early as 5 min after extradural injection in patients receiving systemic phenylephrine; this was unexpected.

The mechanism whereby i.v. adrenaline reduced peak plasma concentrations of bupivacaine was not assessed in this study, but there are several possible explanations. Adrenaline may increase clearance of bupivacaine by increasing hepatic blood flow. Although this has been shown to occur with lignocaine (extraction ratio 0.9), uptake of bupivacaine by the liver is less sensitive to changes in liver blood flow (extraction ratio 0.2) [13]. Furthermore, adrenaline added to extradural bupivacaine has been shown to have no effect on the clearance of bupivacaine [14]. For these reasons, enhanced hepatic clearance is unlikely to affect peak plasma concentrations in the first 10 min after extradural injection.

Adrenaline and phenylephrine may have different vasoconstrictor effects on the extradural vasculature which could potentially influence absorption of bupivacaine from the extradural space [7]. However, this seems unlikely in the dosage used. A more plausible explanation is that the systemic effects of adrenaline which maintain cardiac output and increase skeletal muscle blood flow [8, 9] would tend to enhance redistribution of the absorbed bupivacaine to the periphery [10]. In contrast, the patients who received phenylephrine had a reduction in cardiac output. This is associated usually with vasoconstriction in the periphery and a reduction of blood flow in the vessel-rich group, reducing the volume of distribution [1–3, 15]. That we were unable to

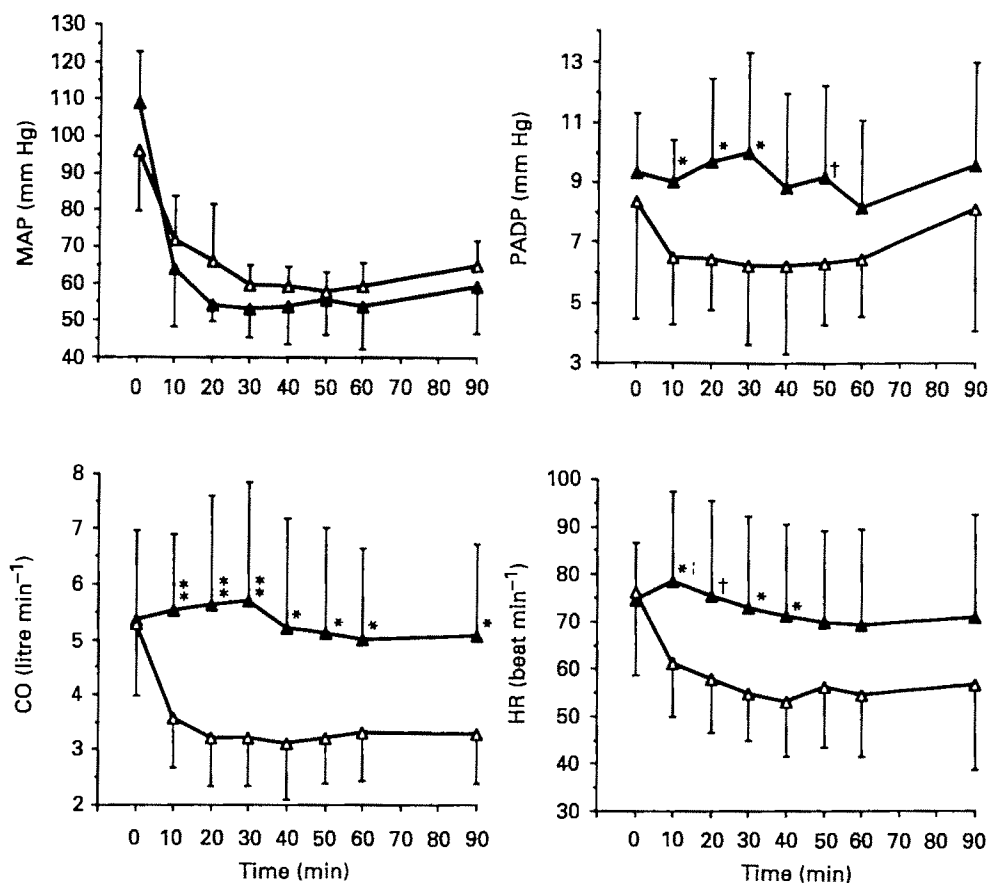


FIG. 2. Haemodynamic changes after extradural injection of 0.75% bupivacaine plain 25 ml in six patients receiving low-dose adrenaline (▲) and nine receiving phenylephrine (△) i.v. infusions (mean, sd). † $P = 0.05$; * $P < 0.05$; ** $P < 0.01$.

demonstrate a strong correlation between cardiac output and circulating concentrations of bupivacaine suggests that other factors such as the effects of adrenaline on skeletal muscle blood flow also contribute to the reduction in plasma concentrations of local anaesthetic.

Peak circulating concentrations of local anaesthetic after extradural anaesthesia are reduced when adrenaline-containing local anaesthetics are used [10, 11]. A reduction in uptake from the site of injection secondary to vasoconstriction has been demonstrated [16]. However, Tucker suggested that systemic effects of adrenaline could also reduce concentrations of local anaesthetic after extradural block by increasing the volume of distribution and hepatic blood flow [10]. Our observations would tend to support this, as increased cardiac output with i.v. adrenaline was associated with reduced circulating concentra-

tions of bupivacaine. It would appear, therefore, that the reduction in circulating concentrations of local anaesthetic after injection of adrenaline-containing anaesthetic was caused by both local and systemic effects of the adrenaline.

Although 25 ml of the 30 ml of bupivacaine was injected into the extradural space, 5 ml was infiltrated into the paravertebral muscles. The arterial concentrations of bupivacaine reported therefore do not reflect only reabsorption from the extradural space. In all likelihood, the effect of different vasopressors on peak circulatory concentrations of local anaesthetic applies to other regional anaesthetic techniques.

Therapeutic benefits of i.v. adrenaline infusions after extradural anaesthesia include a reduction in circulating concentration of local anaesthetic, a reduction in the frequency of reflex bradycardia [17, 18] and preservation of cardiac output even

when mean arterial pressure decreases [6, 7, 18]. These effects have been observed also with adrenaline injected into the extradural space, but they tend to last for only 30–40 min [7, 18]. For this reason, we recommend that, if large doses of local anaesthetic are used to achieve extensive neural block to provide intraoperative hypotension, i.v. infusions of adrenaline are used to provide circulatory support throughout the anaesthetic.

REFERENCES

1. Benowitz N, Forsyth RP, Melmon KL, Rowland M. Lidocaine disposition kinetics in monkey and man. I. Prediction by a perfusion model. *Clinical Pharmacology and Therapeutics* 1974; 16: 87–98.
2. Thomson PD, Melmon KL, Richardson JA, Cohn K, Steinbrunn W, Cudihee R, Rowland M. Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. *Annals of Internal Medicine* 1973; 78: 499–508.
3. Chow MS, Ronfeld RA, Hamilton RA, Helmink R, Fieldman A. Effect of external cardiopulmonary resuscitation on lidocaine pharmacokinetics in dogs. *Journal of Pharmacology and Experimental Therapeutics* 1983; 224: 531–537.
4. Covino BG. Toxicity and systemic effects of local anesthetic agents. In: Strichartz GR, ed. *Local Anesthetics*. Berlin: Springer-Verlag, 1987; 187–212.
5. Engberg G, Wiklund L. The use of ephedrine for prevention of arterial hypotension during epidural blockade. A study of the central circulation after subcutaneous premedication. *Acta Anaesthesiologica Scandinavica* 1978; 66 (Suppl.): 1–26.
6. Sharrock NE, Mineo R, Urquhart B. Hemodynamic response to low-dose epinephrine infusion during hypotensive epidural anesthesia for total hip replacement. *Regional Anesthesia* 1990; 15: 295–299.
7. Stanton-Hicks M, Berges PU, Bonica JJ. Circulatory effects of peridural block. IV. Comparison of the effects of epinephrine and phenylephrine. *Anesthesiology* 1973; 39: 308–314.
8. Freyschuss U, Hjemdahl P, Juhlin-Dannfelt A, Linde B. Cardiovascular and metabolic responses to low dose adrenaline infusion: an invasive study in humans. *Clinical Science* 1986; 70: 199–206.
9. Stratton JR, Pfeiffer MA, Ritchie JL, Halter JB. Hemodynamic effects of epinephrine: concentration-effect study in humans. *Journal of Applied Physiology* 1985; 58: 1199–1206.
10. Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetics. *Clinical Pharmacokinetics* 1979; 4: 241–278.
11. Tucker GT, Mather LE. Properties, absorption and disposition of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia: JB Lippincott, 1988; 47–110.
12. Cousins MJ, Bromage PR. Epidural neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia: J. B. Lippincott, 1988; 277–285.
13. Bowdle TA, Freund PR, Slattery JT. Propanolol reduces bupivacaine clearance. *Anesthesiology* 1987; 66: 36–38.
14. Burm AGL, van Kleef JW, Gladines MPRR, Olthof G, Spierdijk J. Epidural anesthesia with lidocaine and bupivacaine: effects of epinephrine on the plasma concentration profiles. *Anesthesia and Analgesia* 1986; 65: 1281–1284.
15. Benowitz NL, Meister W. Clinical pharmacokinetics of lignocaine. *Clinical Pharmacokinetics* 1978; 3: 177–201.
16. Burfoot MF, Bromage PR. The effects of epinephrine on mepivacaine absorption from the spinal epidural space. *Anesthesiology* 1971; 35: 488–492.
17. Green DST, Quinn TJ, Urquhart B, Sharrock NE. Severe bradycardia during epidural anesthesia. *Anesthesiology* 1989; 71: A91.
18. Bonica JJ, Kennedy WF, Akamatsu TJ, Gerbershagen HU. Circulatory effects of peridural block: 3. Effects of acute blood loss. *Anesthesiology* 1972; 36: 219–227.

COMPARISON OF PLAIN AND ALKALINIZED LOCAL ANAESTHETIC MIXTURES OF LIGNOCAINE AND BUPIVACAINE FOR ELECTIVE EXTRADURAL CAESAREAN SECTION

R. FERNANDO AND H. M. JONES

SUMMARY

We have examined a local anaesthetic mixture of 0.5% bupivacaine 10 ml and 2% lignocaine 10 ml with adrenaline 1 in 200 000, to which 8.4% sodium bicarbonate 2 ml was added, for extradural Caesarean section. The alkalized mixture of local anaesthetics produced a block of more rapid onset and density than a mixture of bupivacaine and lignocaine alone ($P < 0.001$).

KEY WORDS

Anaesthesia: obstetric. Anaesthetics, local: alkalized mixture, bupivacaine, lignocaine. Anaesthetic techniques: extradural.

The use of extradural block for Caesarean section has three main disadvantages: a slow onset time commonly ranging from 20 to 50 min to achieve a sensory block from T4 to S5 [1-3], a density of block not comparable to that of spinal anaesthesia [4] and, occasionally, a need for inducing general anaesthesia. Large volumes of local anaesthetic may be used, exceeding the recommended dose [5].

Spinal anaesthesia offers the advantages of rapid onset and good quality [6, 7], but postdural puncture headache remains a disadvantage, even with 26-gauge spinal needles [6]. Thirty-gauge needles may reduce the incidence of headache, but may be associated with technical difficulties [8]. Pencil point needles are said to separate dural fibres and to reduce the incidence of headache [9].

Extradural block for obstetric anaesthesia would be enhanced if a local anaesthetic agent were available which provided a block of rapid onset, good quality and of adequate duration using the minimum dose, so that toxicity is avoided [5, 10-12].

Plain 0.5% bupivacaine and 2% lignocaine with adrenaline 1 in 200 000 are popular agents for extradural Caesarean section [12, 13], but the former has potential cardiotoxicity and the latter provides poor quality extradural block [14, 15]. Mixtures of local anaesthetics have obvious advantages and have been used for several years in non-obstetric practice [16]. The dose of bupivacaine may be reduced, thereby reducing cardiotoxicity [17].

Recently, Howell and colleagues have used a mixture of 2% lignocaine 10 ml and 0.5% bupivacaine 10 ml to which adrenaline had been added to achieve a concentration of 1 in 200 000 for obstetric use [14]. However, the onset time for this mixture (T4-S5 sensory block) did not differ significantly from that of three other solutions (mean onset time 24.6 min).

There is some evidence to suggest that alkalizing local anaesthetic solutions results in improved efficacy, by increasing the amount of lipid soluble form in solution [18]. We have therefore examined the use of an alkalized mixture of lignocaine and bupivacaine in extradural block for Caesarean section.

PATIENTS AND METHODS

We prepared a solution of 2% lignocaine 10 ml and 0.5% bupivacaine 10 ml to which 0.1 ml of adrenaline 1 in 1000 was added to achieve a con-

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centration of 1 in 200 000. We then added 0.5-ml aliquots of 8.4% sodium bicarbonate to this mixture to optimize the pH without causing precipitation. pH was measured using a Kent E1L 7035 electrode subjected to a two-point calibration using commercially available buffered pH solutions.

The final mixture consisted of 2% lignocaine 10 ml and 0.5% bupivacaine 10 ml, 0.1 ml of adrenaline 1 in 1000 and 2 ml of 8.4% sodium bicarbonate.

After Ethics Committee approval and informed patient consent had been obtained, we studied 20 healthy women undergoing elective Caesarean section. They were allocated randomly in a double-blind design to receive one of two solutions: a 50:50 mixture of 0.5% bupivacaine and 2% lignocaine with adrenaline 1 in 200 000 to which 8.4% sodium bicarbonate 2 ml had been added, or a 50:50 mixture of 0.5% bupivacaine and 2% lignocaine with adrenaline 1 in 200 000 to which 2 ml of normal saline had been added. One millilitre of each solution was kept for pH analysis at the end of the procedure. Hence 21 ml of each solution was used initially. All solutions were used at room temperature.

The anaesthetist responsible for the conduct of the extradural block prepared the initial solution of 2% lignocaine 10 ml, 0.5% bupivacaine 10 ml and 0.1 ml of adrenaline 1 in 1000. A second anaesthetist who was not involved directly with clinical management or testing of the patient drew up either 2 ml of 8.4% sodium bicarbonate or 2 ml of normal saline, according to the randomization envelopes. The first anaesthetist then added the 2 ml of solution into the previously prepared "20 ml" syringe with the local anaesthetic mixture. At no time was the first anaesthetist aware of the contents of the 2-ml syringe given to him. One millilitre of this final solution was withdrawn from the syringe and kept for pH analysis.

After routine prophylaxis with ranitidine and oral antacid, cannulation of a vein and attachment of non-invasive cardiovascular monitoring, the patient was placed in the sitting position. The extradural space was located by a 16-gauge Tuohy needle at the L2-3 or L3-4 interspace using loss of resistance to air and 3 cm of catheter was left in the extradural space. After an i.v. preload of Hartmann's solution 1 litre, 3 ml of the extradural solution was injected through the catheter with the patient in the left lateral position. After 5 min,

TABLE I. *Bromage motor block*

1—No block	Full flexion of knees and feet.
2—Partial block	Just able to flex knees, but still full flexion of feet possible.
3—Almost complete block	Unable to flex knees, flexion of feet possible.
4—Complete block	Unable to flex knees or feet.

with no sign of catheter misplacement, another 18 ml of test solution was injected over 2 min. The onset of sensory block was assessed every 1 min by loss of cold sensation to ethyl chloride spray, and motor block by the loss of leg muscle power on a four-point Bromage Scale (table I). The position of the patient was changed as deemed appropriate to achieve a bilateral sensory block (T4-S5) as quickly as possible. Finally, the patient was turned supine with left lateral tilt when the sensory block was adequate. If, 15 min after the end of the main injection of 18 ml, the thoracic or sacral level was considered inadequate, further increments of a 50:50 mixture of 2% lignocaine and 0.5% bupivacaine with adrenaline 1 in 200 000 were given, and the patient's position changed if necessary.

In all patients, ephedrine 30 mg was added to the third 500-ml container of Hartmann's solution. Hypotension was minimized by infusing this solution to ensure the systolic arterial pressure was maintained greater than 100 mm Hg.

An upper sensory level of T4 and a lower level of S5 were considered adequate for surgery. The onset time was defined as the time from giving the test dose to the patient being ready for surgery. Any pain or discomfort during the procedure was treated with supplementary extradural solution and i.v. or extradural opioids after delivery of the baby.

Fentanyl 100 µg in 8 ml of normal saline was administered via the extradural catheter at the completion of surgery for postoperative pain relief. At the end of the procedure, both anaesthetist and patient were asked to answer preset questions to evaluate the extradural block. The anaesthetist rated the quality of the block as follows: excellent = no pain or discomfort felt; very good = only mild discomfort was felt, not requiring treatment; good = pain or discomfort requiring further local anaesthetic or extradural fentanyl; fair = in addition to further local an-

aesthetic and extradural fentanyl, i.v. alfentanil 0.2 mg was required; poor = general anaesthesia had to be induced.

Statistical analysis

To compare the sensory and motor block onset times between the two groups, a Mann-Whitney test was used. Fisher Exact test was used to evaluate tables IV and V. $P < 0.05$ was regarded as statistically significant.

RESULTS

The groups were comparable in age, weight, height and duration of surgery (table II).

There was a statistically significant difference ($P < 0.001$) between the two groups for onset time to sensory block T4-S5. Mean sensory onset time in the pH adjusted group was 12.7 (SD 1.16) min (range 10–14 min), whereas that in the control group was 21.9 (6.47) min (range 13–38 min). The onset time to Bromage Scale 3 motor block was also significantly faster in the pH adjusted group ($P < 0.002$). The mean time in the alkalized group was 15.5 (1.27) min (range 14–18 min), compared with 24.5 (6.38) min (range 15–40 min) in the control group (table III). The highest block in both groups was T2.

TABLE II. Patient data (mean (SD))

	Alkalized group (n = 10)	Plain group (n = 10)
Age (yr)	26.3 (3.16)	28.2 (4.26)
Height (cm)	158.9 (5.62)	158.7 (5.40)
Weight (kg)	74.8 (11.25)	70.5 (9.34)
Duration of surgery (min)	54.9 (14.33)	41.4 (12.47)

TABLE III. Onset times for sensory and Bromage Scale 3 motor block. * $P < 0.001$ compared with plain group sensory block; ** $P < 0.002$ compared with plain group motor block

	Patient number										Mean
	1	2	3	4	5	6	7	8	9	10	
Alkalized group											
Sensory onset (min)*	12	13	13	14	13	14	13	12	13	10	12.7
Bromage 3 (min)**	15	14	15	14	17	15	15	16	18	16	15.5
pH	7.12	7.12	7.20	7.10	7.20	7.20	7.25	7.30	7.30	7.25	
Plain group											
Sensory onset (min)	17	20	20	13	21	21	22	23	24	38	21.9
Bromage 3 (min)	20	22	25	15	23	26	25	23	26	40	24.5
pH	5.30	4.70	4.90	5.00	4.60	4.60	5.00	4.90	5.10	5.00	

TABLE IV. Number of patients in each group experiencing pain or discomfort during their Caesarean section

	Alkalized group	Plain group
None	10	4
Mild	0	2
Moderate	0	4
Severe	0	0

TABLE V. Anaesthetist's assessment of the extradural block

	Alkalized group	Plain group
Excellent	10	4
Very good	0	2
Good	0	2
Fair	0	2
Poor	0	0

Only 21 ml of local anaesthetic solution was used for all 10 patients in the pH adjusted group, whereas three patients in the control group required supplementary local anaesthetic to achieve a sensory block to T4. There was no symptomatic evidence of systemic toxicity in any patient.

None of the patients in the pH-adjusted group felt any pain or discomfort during the procedure ($P = 0.011$) (table IV). Six patients in the control group required supplementation.

Assessment of the extradural block by both the anaesthetist and the patient was completed at the end of the procedure. All 10 patients in the pH-adjusted group were rated as excellent by the anaesthetist ($P = 0.011$) (table V). All 20 patients were highly satisfied with their extradural block.

In both groups, cardiovascular stability was achieved with the crystalloid preload and the ephedrine infusion.

All the babies delivered had Apgar scores greater than 7 at 1 min and 9 or more at 5 min. None needed resuscitation.

The pH of each solution was tested using a digital pH meter at the end of the procedure. The average pH of the alkalized group was 7.20 (range 7.10–7.30); that of the control group was 4.91 (range 4.60–5.30) ($P < 0.001$).

DISCUSSION

Alkalization of local anaesthetic solutions to speed up the onset of action has been used with varying degrees of success by several workers [18–20]. Another method to reduce the onset time has been the production of carbonated solution [21–23]. For example, lignocaine has been acidified by carbonation and is produced commercially by Astra Pharmaceuticals. Early work by Bromage indicated the superiority of such carbonated solutions compared with plain lignocaine in open studies in which a single local anaesthetic bolus was injected [22, 23]. Alkalized solutions of 2% lignocaine with adrenaline 1 in 400 000 were compared with plain and carbonated lignocaine solutions for elective Caesarean section by Liepert and colleagues [21], who did not find any significant difference in the onset times (approximately 20 min) for all three groups. However, an incremental technique was used to deliver the local anaesthetic into the extradural space.

We chose to use a bolus technique after a test dose had been given, as differences in onset times should be more apparent than with an incremental method. We found that the alkalized mixture consistently had a more rapid onset of action which often reduced the waiting time to surgery by 50%. In addition, the extradural block was thought to be extremely dense in nature and provided good operating conditions without any patient experiencing pain or discomfort during the procedure. The onset times for the control mixture were comparable to those reported by Howell and colleagues [14].

Routine use of such a mixture has some disadvantages, including a potential for error in mixing four different drugs and unknown stability of the resultant solution. At present we mix the solutions immediately before use, as we have no data on the stability of this alkalized mixture.

However, alkalized solutions of bupivacaine and adrenaline have been shown to be stable for up to 6 h [24]. It has been suggested that sodium bicarbonate might be added to a premixed syringe of bupivacaine and lignocaine with adrenaline 1 in 200 000 using an IMS (International Medication System) type of cartridge.

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REFERENCES

1. Laishley RS, Morgan BM. A single dose epidural technique for Caesarean section. A comparison between 0.5% bupivacaine plain and 0.5% bupivacaine with adrenaline. *Anaesthesia* 1988; 43: 100–103.
2. Thorburn J, Moir DD. Epidural analgesia for elective Caesarean section technique and its assessment. *Anaesthesia* 1980; 35: 3–6.
3. Paech MJ, Westmore MD, Speirs HM. A double-blind comparison of epidural bupivacaine and bupivacaine/fentanyl for Caesarean section. *Anaesthesia and Intensive Care* 1990; 18: 22–30.
4. Russell IFC. Spinal is better than epidural anaesthesia for elective Caesarean section. In: Morgan B, ed. *Controversies in Obstetric Anaesthesia*. Sevenoaks: Edward Arnold, 1990; 1–11.
5. Crawford JS, Davies P, Lewis M. Some aspects of epidural block provided for elective Caesarean section. *Anaesthesia* 1986; 41: 1039–1046.
6. Michie AR, Freeman RM, Dutton DA, Howie HB. Subarachnoid anaesthesia for elective Caesarean section. A comparison of two hyperbaric solution. *Anaesthesia* 1988; 43: 96–99.
7. Russell IF, Holmquist EL. Subarachnoid analgesia for Caesarean section. A double-blind comparison of plain and hyperbaric 0.5% bupivacaine. *British Journal of Anaesthesia* 1987; 59: 347–353.
8. Lesser P, Bembridge M, Lyons G, Macdonald R. An evaluation of a 30-gauge needle for spinal anaesthesia for Caesarean section. *Anaesthesia* 1990; 45: 767–768.
9. Cesarini M, Torrielli R, Lahave F, Mene JM, Cabiro C. Sprotte needle for intrathecal anaesthesia for Caesarean section: incidence of postdural puncture headache. *Anaesthesia* 1990; 45: 656–658.
10. Albright GA. Cardiac arrest following regional anaesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; 51: 285–287.
11. Marx GF. Cardiotoxicity of local anaesthetics. *Anesthesiology* 1984; 60: 3–5.
12. Abboud TK, Kim KC, Noueihed R, Kuhnert BR, Der Mardirossian N, Moundjian J, Sarkis F, Nagappala S. Epidural bupivacaine, chlorprocaine or lidocaine for Cesarean section—maternal and neonatal effects. *Anaesthesia and Analgesia* 1983; 62: 914–919.

13. Paech MJ. Epidural anaesthesia for Caesarean section: a comparison of 0.5 % bupivacaine and 2 % lignocaine both with adrenaline. *Anaesthesia and Intensive Care* 1988; 16: 187-196.
14. Howell P, Davies W, Wrigley M, Tan P, Morgan B. Comparison of four local extradural anaesthetic solutions for elective Caesarean section. *British Journal of Anaesthesia* 1990; 65: 648-653.
15. Scott DB, Hibbard BM. Serious non-fatal complications associated with extradural block in obstetric practice. *British Journal of Anaesthesia* 1990; 64: 537-541.
16. Seow LT, Lips FG, Cousins MJ, Mather LE. Lidocaine and bupivacaine mixtures for epidural blockade. *Anesthesiology* 1982; 56: 177-183.
17. De Jong RH, Bonin JD. Mixtures of local anesthetics are no more toxic than the parent drugs. *Anesthesiology* 1981; 54: 177-181.
18. McMorland GH, Douglas MJ, Jeffrey WK, Ross PLE, Axelson JE, Kim JHK, Gambling DR, Robertson K. Effect of pH adjusted bupivacaine on onset and duration of epidural analgesia in parturients. *Canadian Journal of Anaesthesia* 1986; 33: 537-541.
19. Difazio CA, Carron H, Grosslight KR. Comparison of pH adjusted lidocaine solutions for epidural anesthesia. *Anesthesia and Analgesia* 1986; 65: 760-764.
20. Tackley RM, Coe AJ. Alkalinised bupivacaine and adrenaline for epidural Caesarean section. *Anaesthesia* 1988; 43: 1019-1021.
21. Liepert DJ, McMorland GH, Gambling DR, Kim HK, Ross PLE. Comparison of lidocaine CO₂, 2% lidocaine hydrochloride, and pH adjusted lidocaine hydrochloride for Caesarean section anaesthesia. *Canadian Journal of Anaesthesia* 1990; 37: 333-336.
22. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiologica Scandinavica* 1965; (Suppl. 16): 55-69.
23. Bromage PR. Improved conduction blockade in surgery and obstetrics: carbonated local anaesthetics. *Canadian Medical Association Journal* 1967; 97: 1377-1384.
24. Bonhomme L, Benhamou D, Martre H, Preaux N. Chemical stability of bupivacaine and epinephrine in pH adjusted solutions. *Anesthesiology* 1987; 67: A279.

PATTERNS OF OXYGENATION AFTER THORACOTOMY

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AND J. G. JONES

SUMMARY

We have studied patterns of oxygen saturation (Sp_{O_2}) before and after thoracotomy in 20 patients monitored nightly from the preoperative night to the fourth postoperative night. After operation, 10 patients received paravertebral bupivacaine (PVB) infusion and 10 received paravertebral saline (PVS) infusion. Papaveretum was given as required. Before operation the Sp_{O_2} profiles formed two groups: stable with $Sp_{O_2} > 94\%$ and stable with a median Sp_{O_2} less than 94% (hypoxaemia). During the first night after operation Sp_{O_2} profiles formed four groups: stable, not hypoxaemic (2/20); stable, hypoxaemic but improving (8/20); stable and constant hypoxaemia (5/20); unstable, hypoxaemic and deteriorating (5/20). Eleven patients remained hypoxaemic as late as the fourth night after operation. All patients who were hypoxaemic before operation were hypoxaemic after operation. Postoperative hypoxaemia was predicted in only 50% of cases. Papaveretum requirement was reduced in the PVB group, but regional analgesia did not affect the proportion of patients showing each Sp_{O_2} profile. Papaveretum caused a decrease in Sp_{O_2} in both analgesic groups.

KEY WORDS

Analgesia: postoperative. Analgesics: papaveretum. Anaesthetic techniques: paravertebral block. Anaesthetics, local: bupivacaine. Hypoxia: perioperative.

Recent advances in the presentation of data obtained from continuous pulse oximetry have involved the use of computers to produce graphic representations of the distribution pattern of oxygen saturation (Sp_{O_2}). Initial studies using this approach have described patterns of hypoxaemia in patients undergoing lower abdominal surgery,

which showed unstable hypoxaemia with a wide distribution of Sp_{O_2} , associated with sleep and administration of opioid [1]. In contrast, thoracotomy is a major surgical procedure which is likely to lead to considerable changes in pulmonary function. Incomplete lung re-expansion, reduced chest wall and diaphragmatic activity caused by pain may result in atelectasis and hence intrapulmonary shunting. It has already been shown that regional anaesthesia after thoracotomy reduces pain scores, promotes more rapid return of pulmonary function and reduces opioid requirement [2, 3]. The aim of this study was to use continuous pulse oximetry to examine patterns of postoperative hypoxaemia occurring in patients undergoing thoracotomy and to describe the effect on such patterns of regional analgesia and morphine.

PATIENTS AND METHODS

We studied 20 patients (ASA I or II) undergoing elective thoracotomy for repair of hiatus hernia and who were scheduled to take part in a separate study of the metabolic response to thoracotomy. Patients were excluded if they had allergy to bupivacaine, if they underwent a further or more extensive procedure such as thoracoabdominal surgery, if the operation was carried out as an emergency or if long term analgesics were being taken. All patients gave informed consent and approval was obtained from the Hospital Ethics

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Committee. Patients were allocated randomly to two groups, one to receive an infusion of paravertebral bupivacaine (PVB) and the other (control) group to receive an infusion of paravertebral saline (PVS) in the postoperative period. There were 11 females and nine males, the average age was 49.4 yr (range 19–69 yr) and the average weight was 74 kg (range 52–102 kg). There was no difference in age, weight or smoking habits between the groups.

All patients had continuous preoperative overnight oximetry. Premedication was with papaveretum 0.2 mg kg⁻¹ and hyoscine 0.004 mg kg⁻¹ 1 h before operation. The patients were anaesthetized with thiopentone 5 mg kg⁻¹, vecuronium 0.1 mg kg⁻¹ with additional intermittent boluses, phenoperidine 2 mg, nitrous oxide and isoflurane. End-tidal carbon dioxide partial pressure was kept between 3 kPa and 4 kPa and oxygen saturation kept greater than 90% throughout. Before closure of the wound, an 18-gauge Portex extradural catheter was sited by direct vision subpleurally in the paravertebral space.

Patients in the PVB group received 0.5% bupivacaine 20 ml through the catheter before closure of the chest, followed by a postoperative infusion of 0.5% bupivacaine at a rate of 0.1 ml kg⁻¹ h⁻¹. This was continued for 5 days. Patients in the PVS group received equivalent volumes of normal saline for the same period. The anaesthetist, nurses, ward doctors and patient were unaware of the nature of the infusion. Papaveretum was prescribed 4-hourly at suitable doses for all patients and was given by the nurses when required. For the first 24 h oxygen (24% by Ventimask) was prescribed to be administered for 30 min only if the Sp_{O₂} decreased to less than 85% for 1 min. On subsequent nights the pulse oximeter alarms were disabled and oxygen given only if indicated clinically. On arrival at the ward, patients were connected to the pulse oximeter with the probe on the right or left index finger and were monitored for the rest of the day of operation and for the first night after operation until 09:00 the next day. Further oximetry was carried out for three further nights (a total of four postoperative nights) from 21:00 to 09:00. Records were taken of the timings of doses of i.m. papaveretum and the administration of oxygen.

Oximetry

Continuous monitoring of Sp_{O₂} was carried out using a Datascope Accusat Pulse Oximeter which

was interfaced with an Amstrad IBM-compatible portable microcomputer. Recordings of Sp_{O₂} were made every 15 s and stored so that 240 samples were collected for every 60 min. The program eliminated all erroneous readings. The number of these could be ascertained and were not numerous. The results were analysed as follows. Compressed Sp_{O₂} distribution diagrams were plotted for each study period. Each curve represents a data collection interval of 1 h and the height of the curve at each saturation value represents the percentage of the hour spent at that saturation. Curves for subsequent 1-h epochs were stacked sequentially. These data were analysed visually for pattern and trend. Patterns of tall, well-superimposed peaks were classed as stable. Patterns of flat peaks with much variation from hour to hour were classed as unstable. In addition, a computer routine was used to analyse the data. From the distribution of the data within each interval, the median Sp_{O₂} was calculated. The 50th centile was calculated for each epoch over the study period. As each data collection interval was 1 h in duration, the 20th centile represents 12 min spent at oxygen saturations less than this value. In this study we defined hypoxaemia as occurring when the 20th centile was equal to or less than an Sp_{O₂} of 94%, that is, 12 min or more per hour spent with an Sp_{O₂} equal to or less than 94%—a value based on our previous study of normal subjects [1]. It was felt, however, that the use of the 20th rather than the 10th centile (12 min rather than 6 min per hour) gave a more significant indication of the degree of hypoxaemia. As a method of quantifying the duration of hypoxaemia, the duration of time was calculated for each night of oximetry that the 20th centile was at less than Sp_{O₂} 94% and, where applicable, less than Sp_{O₂} 90%. Using least squares linear regression, the effect of age and weight was compared with the duration of postoperative hypoxaemia on the first night.

RESULTS

Patterns of oxygen saturation

Night before operation. Eleven of 20 patients were stable and not hypoxaemic (fig. 1A). Four of 20 patients were stable but showed hypoxaemia for less than 3 h. Five patients were hypoxaemic for the majority of the night with some mild instability whilst asleep (fig. 1B). In one of these,

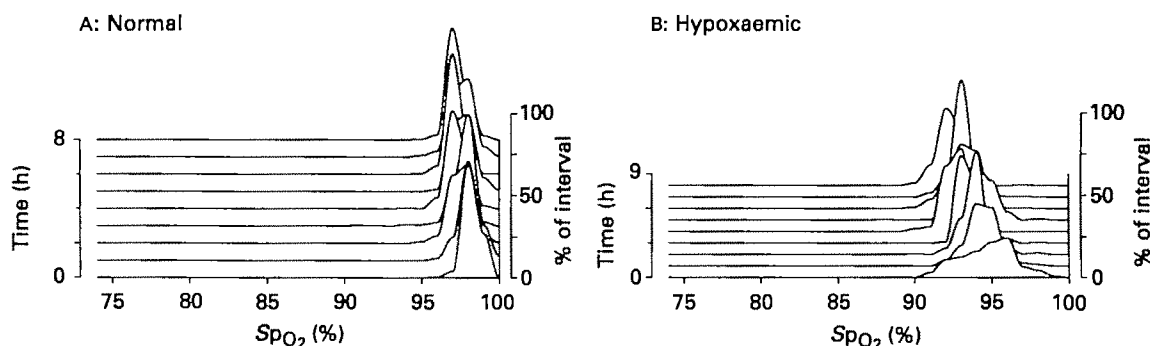


FIG. 1. A: Normal preoperative compressed Sp_{O_2} distribution diagram over an 8-h night-time monitoring period. There are tall narrow peaks well clustered together, closely superimposed on one another. Time = elapsed time from 21:03. B: Hypoxaemic preoperative compressed Sp_{O_2} distribution diagram in a similar night-time monitoring period. Peaks are flatter and wider, varying from hour to hour over a range of smaller Sp_{O_2} values. Time = elapsed time from 20:51.

an obese asthmatic, the 20th centile was less than 90 % for 4 h.

First postoperative day and night. Four distinct Sp_{O_2} profiles were observed. The number of patients exhibiting each pattern were similar in the PVS and PVB groups.

Pattern A (fig. 2A): Stable and not hypoxaemic. Seen in 2/20 patients. Both of these patients had been stable with no hypoxaemia before operation.

Pattern B (fig. 2B): Stable and hypoxaemic but with an improving Sp_{O_2} . Seen in 8/20 patients.

Pattern C (fig. 2C): A stable but hypoxaemic pattern shown by 5/20 patients. Three of these patients displayed impaired control with hypoxaemia after i.m. papaveretum.

Pattern D (fig. 2D): Unstable pattern with progressive decrease in oxygen saturation. Seen in 5/20 patients, one of whom was an obese asthmatic displaying a hypoxaemic pattern with poor ventilatory control.

All patients who were hypoxaemic before operation were also hypoxaemic after operation. All five patients who were hypoxaemic for most of the preoperative night spent the whole of the first night after operation with the 20th centile of Sp_{O_2} < 94 %, and three of these spent most of the night with the 20th centile < 90 %. However, another nine patients were hypoxaemic after operation in the absence of any preoperative hypoxaemia. When the duration of hypoxaemia was compared with weight and age using least squares linear regression, a general trend was found as expected, but the correlation coefficients were 0.4 and 0.5, respectively.

Second night after operation. Fifteen patients regained a stable Sp_{O_2} profile, but only three of these had returned to preoperative oxygen saturations. The remaining five patients, all of whom had been unstable on the first night after operation, continued to display an unstable pattern on the second night.

Fourth night after operation. All the patients regained a stable pattern or showed only minor instability. In the PVB group all patients had Sp_{O_2} less than their preoperative values. In the PVS group, however, three of the nine patients studied showed a return of Sp_{O_2} to preoperative values. Eleven of the 16 patients studied on the fourth night after operation were hypoxaemic most of the night. Two of the remaining five had not regained preoperative values.

Table I shows the numbers of patients showing each Sp_{O_2} profile on the night before operation and on the first, second and fourth nights after operation.

Administration of papaveretum

Patients in the PVS group received a larger number of doses of papaveretum (32 doses, total dose 525 mg) than those in the PVB group (20 doses, total dose 300 mg). As most patients received at least one dose irrespective of group, no overall correlation was noted between papaveretum dosage and the Sp_{O_2} patterns described. On an individual basis, however, loss of control and episodes of hypoxaemia were often seen during the hours after administration of papaveretum. Twelve patients showed oxygen de-

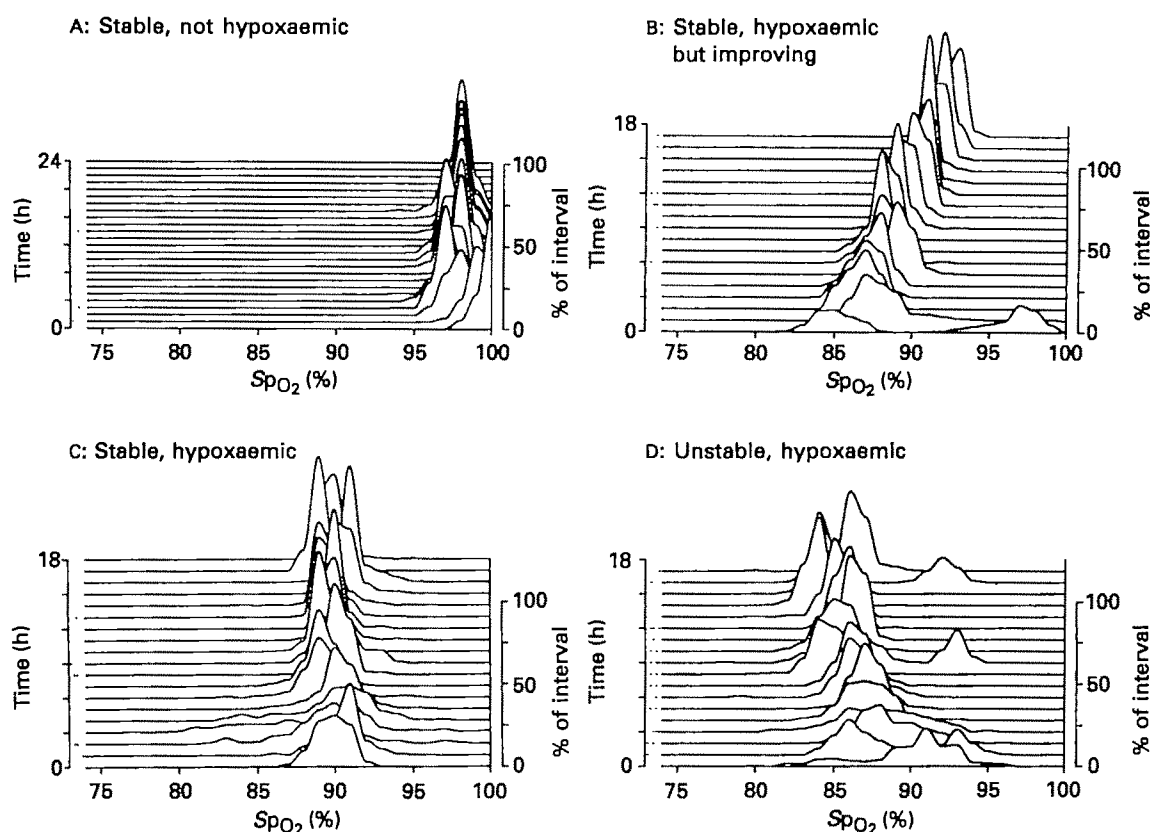


FIG. 2. The four patterns of Sp_{O_2} distribution seen after operation. A: Stable, not hypoxaemic, normal oxygen saturation with narrow superimposed peaks indicative of good ventilatory control. B: Stable, hypoxaemic but improving. The low Sp_{O_2} with broad peaks immediately after operation implies venous admixture as a result of atelectasis in addition to impaired control. Both effects show resolution during the monitoring period. Note the period of oxygen administration in the first 1 h. C: Stable, hypoxaemic. A hypoxaemic pattern caused by V/Q mismatch, with good ventilatory control. D: Unstable, hypoxaemic. Abnormal control and increased venous admixture throughout the period of monitoring. Time = elapsed time from 12:33, 13:35, 11:55 and 12:15, respectively (A-D).

TABLE I. Numbers of patients showing each of the four Sp_{O_2} patterns on the preoperative night and the first, second and fourth nights after operation

Sp_{O_2} pattern	Night			
	Pre-op.	One	Two	Four
Stable, not hypoxaemic	11	2	3	5
Stable, hypoxaemic but improving	0	8	0	0
Stable, hypoxaemic	9	5	12	11
Unstable, hypoxaemic	0	5	5	0

saturation after premedication (an example is shown in figure 3). Three patients showing pattern C (stable but hypoxaemic) showed a period of loss of stability and hypoxaemia following papaveretum, seen as a broadening of the trace. In three patients with pattern B, the steady improvement in saturation showed a subsequent decline which was directly related to a dose of papaveretum (fig. 3—first postoperative night).

DISCUSSION

Postoperative hypoxaemia is thought to be caused by two factors: a gas exchange abnormality induced during anaesthesia as a result of dependent lung atelectasis and a disturbance in the

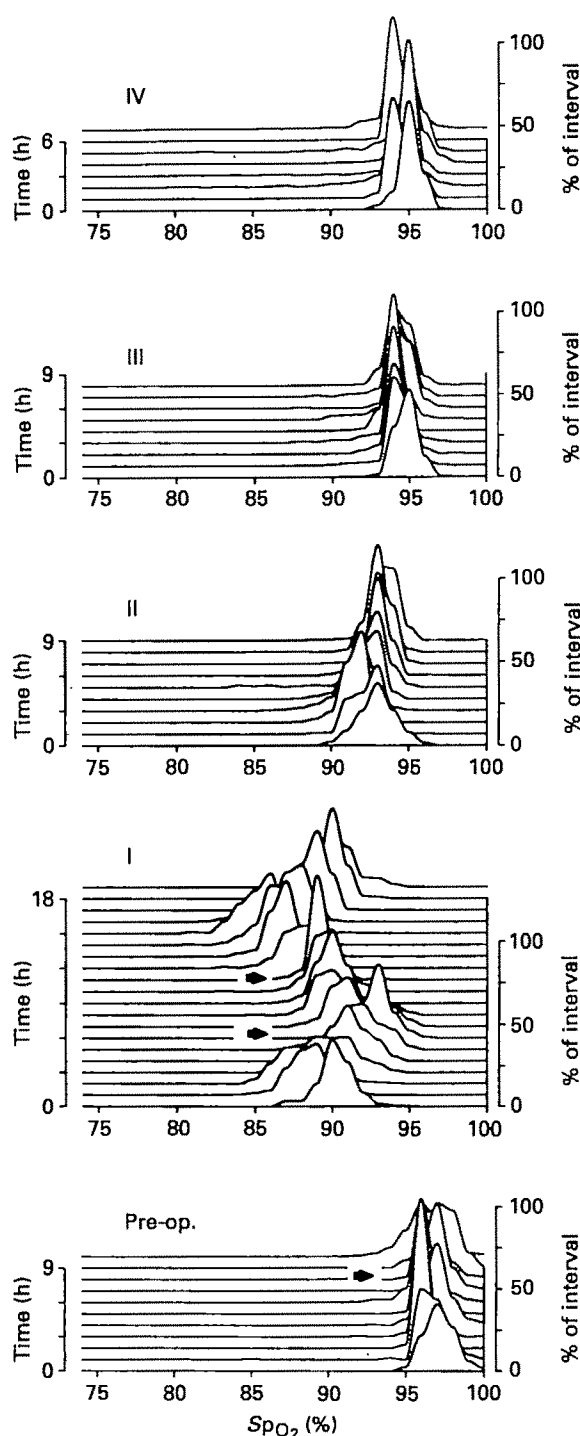


FIG. 3. Changing pattern of SpO_2 over a 5-night monitoring period. Pre-op. = Preoperative night. I-IV = Nights one to four after operation. Arrows indicate doses of i.m. papaveretum. Time = elapsed time.

control of ventilation manifest as episodic obstructive apnoea [4]. Wheatley and colleagues [1] have studied the effect of different analgesic regimens on postoperative hypoxaemia in a group of patients undergoing lower abdominal surgery in which dependent lung atelectasis is less common and hence extrapulmonary factors of more importance. They showed that i.m. and extradural opioids induced an unstable pattern of SpO_2 , with wide rather than peaked curves varying in position from hour to hour. In the present study patients were undergoing thoracotomy in which direct surgical compression, incomplete lung expansion, and reduced chest wall and diaphragmatic movement as a result of pain lead to atelectasis and the development of intrapulmonary shunting.

Observation of the compressed SpO_2 distribution diagrams with classification into different patterns of behaviour seemed to be the most useful way of summarizing these data. When applying numerical analysis to data of this type, it is important to appreciate the non-linear nature of the oxygen dissociation curve at oxygen saturations less than 94% and the fact that the P50 is likely to be different in these patients, especially in view of the wide range of preoperative saturations observed.

An analysis for statistical significance of the difference between SpO_2 arrays using the chi-square test for binned distribution data over the preoperative to first postoperative nights showed a significant difference in most traces: those that did not had a considerable overlap of broad flattened peaks. This is a good example of how the use of compressed SpO_2 distribution diagrams gave more information of this dynamic situation than can be represented in simple numerical form.

Study of the preoperative traces revealed a wider range of oxygen saturations than expected. Of the 50th centiles of SpO_2 for each patient, the median of the sum ranged from 93% to 97%. Nine of 20 patients spent time with the 20th centile of SpO_2 < 94%. This contrasts with our previous study [1] in which the definition of hypoxaemia was based on preoperative nights with a median of 98% with less than 1% of values being < 94%.

Using the criteria for defining hypoxaemia adopted during this study, it was found that hypoxaemia on the first night after operation could be predicted in only 50% of cases. It would be useful to establish criteria which would more accurately predict postoperative hypoxaemia. The

data produced in this study suggest that further work along such lines might reveal enough information for this to be possible.

It is difficult to speculate on the causes of this wide range of preoperative traces. Obviously, the patients' weight and age affect the oxygen saturation. Because of the proximity of the steep part of the oxygen dissociation curve, these patients would be expected to become desaturated more easily after operation. In our study, preoperative hypoxaemia always resulted in postoperative hypoxaemia, but we had a large false negative rate of 50%. In future, improved prediction may be obtained by studying the significance in terms of weights of evidence of a variety of preoperative indicants, including Sp_{O_2} , on postoperative pulmonary dysfunction—for example using the Spiegelhalter–Knill–Jones approach [5]. There was no difference between PVS and PVB groups in the disposition of the different patterns produced nor in the degree of hypoxaemia. Earlier studies in this unit [2, 3] showed improved pain scores and earlier return of preoperative function in PVB patients. However, the administration of i.m. papaveretum to most patients was a confounding factor, as it has been shown to produce an unstable hypoxaemic pattern [1].

It was interesting that two young patients (aged 35 and 19 yr) one of whom had PVS and the other PVB, showed no hypoxaemia at all in the postoperative period and no papaveretum was requested by either.

The traces shown in figures 2B, 2C, 3 and 4 illustrate how oxygen saturation can deteriorate to a low value without loss of control. We interpret this pattern as being almost certainly caused by development of venous admixture resulting from atelectasis. Figure 2C shows how tight control of Sp_{O_2} may be maintained even at low saturations where a wider spread of Sp_{O_2} values might be expected because of the increasing steepness of the oxygen dissociation curve as oxygen saturation decreases. Alterations in ventilatory pattern may be expected not to affect the magnitude of the shunt as changes in lung volume have been shown not to affect $(PA_{O_2} - PA_{O_2})$ [6], and shunt induced by anaesthesia is only partially reversed by PEEP [7]. However, as we did not measure PCO_2 or shunt, we cannot at present ascertain the extent to which hypoventilation and venous admixture contribute to this pattern. Other traces showing hypoxaemia with a wide spread of oxygen saturations (fig. 2b) are likely to be caused by

impairment of ventilatory control. Administration of papaveretum was associated invariably with these periods of impaired control. The effect of opioid premedication in inducing hypoxaemia was notable as this shows the effect of papaveretum without superimposition of the immediate effects of anaesthesia and thoracic surgery.

Compressed Sp_{O_2} distribution diagram plots for two patients over the whole duration of the study are shown in figures 3 and 4. Figure 3 shows a patient with no preoperative hypoxaemia except following opioid premedication at an elapsed time of 8 h (arrow). On the first day and night after operation the hypoxaemic but improving pattern is reversed by i.m. papaveretum at elapsed times of 6 h and 11 h. The progression to the fourth night after operation shows curves becoming steadily more peaked and well superimposed with steadily resolving hypoxaemia, although not achieving preoperative values.

Figure 4 shows a patient who had periods of hypoxaemia on the preoperative night. On the first day and night after operation the pattern becomes progressively more hypoxaemic while the curve peaks become taller and narrower. Islands of greater oxygen saturation are caused by oxygen therapy. On the second night after operation there is further deterioration in oxygen saturation, but the peaks are tall and grouped well together, suggesting significant $\dot{V}/\dot{Q}$ mismatch but good ventilatory control. On the third and fourth nights after operation there is a steady improvement in saturation, but the peaks become less well superimposed and flatter, suggesting a resolving shunt but less effective ventilatory control.

No effort was made to measure sleep, but it was noticed that most traces, including those obtained in the preoperative period, showed a night-time widening of Sp_{O_2} distribution. We have shown previously that profound hypoxaemia after surgery was seen only during sleep, particularly in patients having opioid analgesia [8]. It is known that normal patterns of sleep are severely disrupted in the perioperative period when stages 3, 4 and REM sleep are severely suppressed [9]. A rebound of intense REM sleep occurs about the middle of the first week after operation [10] and it has been shown that hypoventilation and resulting hypoxaemia occur particularly in REM sleep [11].

The trends in the Sp_{O_2} patterns over four consecutive nights after operation showed a gradual improvement in control. However, pre-

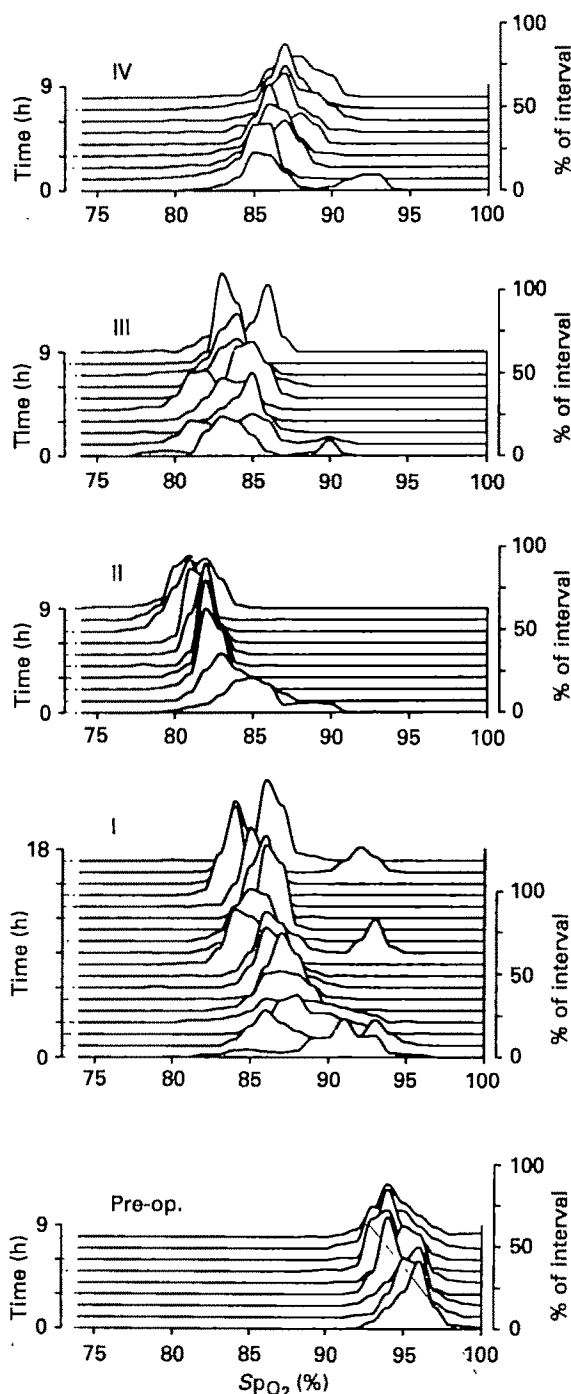


FIG. 4. Changing pattern of Sp_{O_2} over a 5-night monitoring period. Note the Sp_{O_2} is least during the second night. Even after four nights, the Sp_{O_2} distribution is considerably less than the preoperative value (see text). Pre-op. = Preoperative night. I-IV = Nights one to four after operation. Time = elapsed time.

operative values of saturation were not achieved by the fourth night in most patients and this difference from baseline was found to be statistically significant in all instances. In some patients, the degree of hypoxaemia was worse on night two than on the first night after operation (fig. 4). Eight patients in the present study showed an increased instability, signifying a deterioration in ventilatory control on the third and fourth nights after operation, superimposed on the underlying improving trend. This may well have been associated with a rebound of REM sleep.

Oxygen therapy is administered to prevent morbidity from tissue hypoxia. It is common practice to prescribe oxygen on the night following thoracotomy. Our study demonstrated that this is the time when hypoxaemia is most likely to occur. Oxygen therapy is usually only given subsequently if clinically indicated. However, on the second to fourth nights after operation we have demonstrated that a large proportion of patients were still hypoxaemic. This suggests a possible role for the routine monitoring of oxygen saturation after operation in high risk patients or following major operations, or for extending the duration of routine oxygen therapy. More accurate prediction using the techniques described might identify those at risk of postoperative hypoxaemia who would benefit from such manoeuvres. In the meantime, the technique for producing profiles of Sp_{O_2} in the postoperative period provides a new approach to the audit of patients' postoperative behaviour.

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REFERENCES

1. Wheatley RG, Somerville ID, Sapsford DJ, Jones JG. Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. *British Journal of Anaesthesia* 1990; 64: 267-275.
2. Sabanathan S, Bickford-Smith PJ, Pradham GN, Hashimi H, Eng J-B, Mearns AJ. Continuous intercostal nerve block for pain relief after thoracotomy. *Annals of Thoracic Surgery* 1988; 46: 425-426.
3. Sabanathan S, Mearns AJ, Bickford-Smith PJ, Eng J, Berrisford RG, Bibby SR, Majid MR. Efficacy of continuous extrapleural intercostal nerve block on post thoracotomy pain and pulmonary mechanics. *British Journal of Surgery* 1990; 77: 221-225.

4. Jones JG, Sapsford DJ, Wheatley RG. Post-operative hypoxaemia: mechanisms and time course. *Anaesthesia* 1990; 45: 566-573.
5. Seymour DG, Green M, Vaz FG. Making better decisions: construction of clinical scoring systems by the Spiegelhalter-Knill-Jones approach. *British Medical Journal* 1990; 300: 223-226.
6. Heneghan CPH, Bergman NA, Jones JG. Changes in lung volume and (PA_{O_2} - Pa_{O_2}) during anaesthesia. *British Journal of Anaesthesia* 1984; 56: 437-445.
7. Tokics L, Hedenstierna G, Strandberg A, Brismar B, Lundquist H. Lung collapse and gas exchange during general anesthesia: effects of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure. *Anesthesiology* 1987; 66: 157-167.
8. Jordan C, Lehane JR, Robson PJ, Jones JG. Comparison of the respiratory effects of meptazinol, pentazocine and morphine. *British Journal of Anaesthesia* 1979; 51: 497-502.
9. Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: Continuous polygraphic recording of sleep in nine patients receiving post-operative care. *British Medical Journal* 1985; 290: 1029-1032.
10. Knill RL, Moote CA, Skinner MI, Rose EA. Anesthesia with abdominal surgery leads to intense REM sleep during the first post-operative week. *Anesthesiology* 1990; 73: 52-61.
11. Douglas NJ, White DP, Pickett CK, Weil JV, Zwillich CW. Respiration during sleep in normal man. *Thorax* 1982; 37: 840-844.

RIB CAGE CONTRIBUTION TO RESTING AND CARBON DIOXIDE STIMULATED VENTILATION DURING 1 MAC ISOFLURANE ANAESTHESIA

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SUMMARY

Using respiratory inductive plethysmography, we have measured rib cage and abdominal motion during isoflurane anaesthesia in 16 healthy day-surgery patients. Anaesthesia was induced with propofol and maintained with 1 MAC isoflurane in air-oxygen via a laryngeal mask. Measurements were taken during both resting ventilation and hyperpnoea induced by rebreathing carbon dioxide. For resting ventilation, the rib cage contributed a mean (SD) of 33 (15) % of the total ventilation whilst awake, and 39 (12) % during anaesthesia (ns). With increasing end-tidal carbon dioxide whilst awake, the subjects showed a mean increase in the percentage rib cage contribution of 7.1 (12.5) %/kPa of carbon dioxide. With isoflurane anaesthesia, there was significant depression of this rib cage recruitment with the mean contribution decreasing by 3.6 (7.4) % kPa⁻¹ ($P < 0.05$). These results indicate that 1 MAC of isoflurane does not selectively depress rib cage motion, except during carbon dioxide stimulated hyperpnoea.

KEY WORDS

Anaesthetics, volatile: isoflurane. Measurement techniques: respiratory inductive plethysmography. Ventilation: rib cage motion.

A reduction in the motion of the rib cage during general anaesthesia was first described by Snow in 1858, and reported to indicate that "a little more chloroform had been inhaled than was necessary" [1]. Previous authors have described selective depression of intercostal muscle activity as contributing both to depressed ventilation [2] and to the reduction in lung volume [3].

Over the past 20 years, techniques have been developed to measure rib cage and abdominal

motion, first by antero-posterior magnetometers, then circumferential strain gauges, and more recently by measurement of cross-sectional area using respiratory inductive plethysmography (RIP). Both magnetometers [2] and strain gauges [3] have been used to measure rib cage motion during halothane anaesthesia with a tracheal tube; in both studies, general anaesthesia reduced the percentage rib cage contribution to ventilation to approximately 50 % of the awake value. However, other studies with non-inhalation agents have failed to show any reduction in rib cage contribution [4-7], although only one of these used RIP [4].

The rib cage component of the ventilatory response to carbon dioxide during anaesthesia has also been studied previously. With halothane anaesthesia and magnetometers [2], the overall reduction in carbon dioxide response was ascribed almost entirely to depression of rib cage motion. This is in contrast with a study of barbiturate anaesthesia using RIP, in which there was only a modest reduction in rib cage contribution [4].

There are three possible explanations for this difference between studies of inhalation and i.v. anaesthesia. First, selective depression of the rib cage component of ventilation may be unique to inhalation anaesthetics. Second, the depth of anaesthesia is unlikely to be equivalent between studies of halothane and, for example, methohexitone. Finally, Bickler's recent study of methohexitone anaesthesia [4] is the only study so far to

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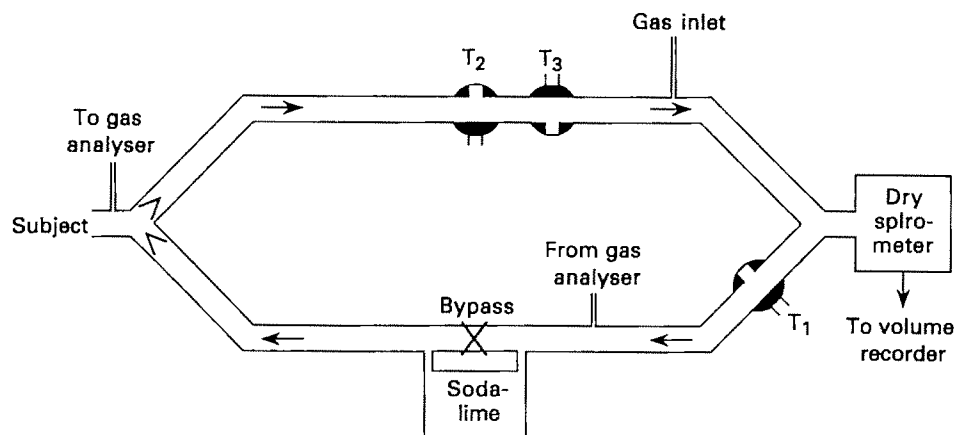


FIG. 1. Apparatus. T_1 , T_2 , T_3 = Taps. See text for further details.

have used RIP, and so the discrepancy seen between studies may simply reflect differences of methodology.

We have therefore used RIP to study ventilation during inhalation anaesthesia, and so have eliminated methodological differences, enabling a valid comparison with Bickler's study. Also, by the use of a laryngeal mask airway instead of a tracheal tube, we have been able to perform the study at 1 MAC with a reliable clear airway, thus eliminating the deep anaesthesia seen with previous studies of inhalation agents.

PATIENTS AND METHODS

Subjects

After approval by the local Ethics Committee and with informed patient consent, we studied 16 male day-case surgical patients immediately before surgery. All were ASA I or II, non-obese (body mass index < 29), and had no history of respiratory disease. Before the study, forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were measured; all values were greater than 80% of values predicted for height and age. ECG, heart rate, end-tidal carbon dioxide concentration and oxygen saturation were monitored throughout the study, and no adverse effects were seen.

Apparatus

The apparatus used for the study is shown in figure 1. This consisted of a circle system with a non-rebreathing valve at the mouthpiece, connected to a dry rolling-seal spirometer (AirCo

Ohio 840), which was calibrated before each subject using a 1.5-litre gas tight syringe. The spirometer gave an electrical volume signal displayed on a chart recorder, from which tidal volume and ventilatory frequency were calculated. A soda-lime canister could be connected to the expiratory limb of the circle for resting ventilation measurements. A separate circuit sampled gas from the mouthpiece and back to the system through a multiple gas analyser (Datex Capnomac) which was calibrated before each subject using gas mixtures supplied by the manufacturer ($48.7 \pm 0.5\%$ oxygen, $4.55 \pm 0.2\%$ carbon dioxide, $2.8 \pm 0.05\%$ enflurane). The gas analyser displayed inspired oxygen concentration, end-tidal carbon dioxide concentration, and inspired/end-tidal isoflurane concentrations. Taps 1 and 2 enabled the subject to breathe air whilst the spirometer was filled or emptied via tap 3 and the gas inlet.

Read's rebreathing method was used to assess the ventilatory response to carbon dioxide [8]. The spirometer was filled to a volume 2 litre more than the subject's vital capacity with 50% oxygen and 7% carbon dioxide in nitrogen. Tap 1 was closed to connect him to the inspiratory side of the circuit, allowing the 2 litre of extra gas in the spirometer to flush the deadspace of the subject and circuit, before tap 2 was switched to complete the circle. Ventilation and PE'_{CO_2} were recorded for 4 min, or until the subject terminated the study because of dyspnoea.

Subjects had their rib cage and abdomen contributions to ventilation measured continuously using respiratory inductive plethysmo-

TABLE I. Subject data and carbon dioxide response lines. BMI = Body mass index; FVC = forced vital capacity, %RC = percentage rib cage contribution to ventilation

Subject No.	Age (yr)	BMI	FVC (litre)	Awake			Anaesthesia		
				Minute volume		%RC Slope	Minute volume		%RC Slope
				Slope	Intercept		Slope	Intercept	
1	26	25	4.73	10.1	5.33	10.8	7.4	5.67	-8.6
2	19	24	4.82	13.4	5.61	14.5	3.2	3.68	2.3
3	28	28	4.13	10.0	5.75	31.1	2.3	3.28	-2.4
4	21	21	3.48	11.4	6.25	-1.4	2.6	5.23	-3.4
5	34	25	3.60	30.7	5.95	5.9	4.7	5.20	8.4
6	18	19	4.50	6.0	5.48	-5.9	4.3	4.35	5.4
7	32	27	4.10	15.7	5.92	3.0	3.7	6.36	7.1
8	43	25	4.61	9.0	5.75	28.1	2.2	3.27	-7.2
9	33	24	3.82	7.4	4.16	6.3	2.6	3.28	-7.4
10	23	23	4.59	14.9	6.01	0.7	8.1	8.47	-8.3
11	35	26	4.06	11.7	6.09	9.7	2.1	4.35	-4.8
12	18	20	4.21	17.9	5.92	4.5	2.0	3.68	-6.5
13	28	25	4.97	8.6	6.33	-10.4	1.1	3.81	0.8
14	26	23	4.34	14.7	5.76	-11.0	5.8	6.21	-8.9
15	40	22	4.69	31.3	6.73	20.4	2.5	5.17	-20.0
Mean	28.2	23.7	4.31	14.2	5.80	7.1	3.6	4.80	-3.6
SD				7.6	0.57	12.5	2.0	1.45	7.4

graphy. Many methods of calibrating RIP have been described, most aimed at measuring tidal volume from the RIP signals without any special manoeuvre being required by the subject. The isovolume technique is a simple method, which requires some coaching of the subject, but is as accurate for measuring rib cage and abdomen contributions to ventilation as the other more complex techniques [9]. The calibration was performed at functional residual capacity with a large isovolume manoeuvre, and the subject remained in the same position throughout the study (including during anaesthesia). Calibration during anaesthesia was not attempted as obtaining an isovolume line by obstructing the airway invalidates the manoeuvre by causing distortion of the rib cage and abdomen compartments. The rib cage and abdomen signals, with analogue signals of carbon dioxide concentration and spirometer volume, were charted on a four-channel chart recorder for later analysis.

Anaesthesia

Subjects received no premedication. Anaesthesia was induced with propofol 3–4 mg kg⁻¹ via an indwelling cannula on the dorsum of the hand, and maintained with isoflurane in an air-oxygen mixture ($F_{I_{O_2}} = 0.5$) with spontaneous ventilation via a laryngeal mask and Mapleson A breathing

system. Overpressure was used to achieve an end-tidal concentration of 1.1–1.2% (1 MAC) as quickly as possible, and this was maintained for 10 min to allow equilibration. Anaesthesia was achieved with the patient connected to the spirometer, by addition of 0.1-ml aliquots of liquid isoflurane to the expiratory limb of the circle. By this means, end-tidal isoflurane concentration was maintained within the limits 1.0–1.2%.

Procedure

The study was performed in the anaesthetic room with subjects in the supine position with the lumbar spine supported by small pillows to minimize spinal movement. Throughout the awake period of the study, patients listened to music through headphones.

The sequence was as follows:

- (1) Calibration of the RIP by the isovolume manoeuvre.
- (2) "Run-in" period with no mouthpiece until regular ventilation returned (as judged by the RIP signal).
- (3) Recording of RIP signals for 1 min with no mouthpiece, allowing the subject to breathe via his natural airway.
- (4) Subject connected to spirometer (including soda-lime) with a mouthpiece/noseclip and a

further run-in period allowed with the subject breathing 50% oxygen.

(5) Resting ventilation and end-tidal carbon dioxide concentration recorded.

(6) Read's rebreathing carbon dioxide response performed.

(7) Subject allowed to recover from the hyperpnoea for 5–10 min.

(8) Anaesthesia induced and stabilized as above.

(9) Rib cage contribution to non-stimulated ventilation recorded with the patient attached to a Mapleson A breathing system.

(10) Non-stimulated ventilation measured with the spirometer circuit connected directly to the laryngeal mask.

(11) Read's rebreathing carbon dioxide response repeated.

Data processing

The rebreathing runs were divided into six to eight periods (each lasting 30 s), depending on the length of the run. For each period (including the resting ventilation) the ventilatory frequency, tidal volume (V_T) at ATPS, minute volume ($\dot{V}_E$) at ATPS, end-tidal carbon dioxide concentration, and percentage rib cage contribution (%RC) to ventilation was calculated. All volumes were converted to BTPS using measured room temperature and assuming the body temperature of all subjects was 37 °C.

For the carbon dioxide ventilation response, $\dot{V}_E$ (litre min^{-1}) was plotted against $P_{E'}\text{CO}_2$ (kPa). Using least squares linear regression, straight lines were fitted to all the data for both awake and anaesthetized carbon dioxide responses in each subject. The mean slope for all subjects was determined and a line of this slope drawn through the grand mean point. The line was plotted between points on the X-axis representing the mean $P_{E'}\text{CO}_2$ for all subjects at the beginning and end of each run.

Similarly, the data for %RC contribution to tidal volume were plotted against $P_{E'}\text{CO}_2$, straight lines derived and overall response lines drawn as above.

To allow comparison with other studies, the data for the rebreathing runs were processed in two different ways:

(1) Each value for $\dot{V}_E$ was divided into the minute volume resulting from either rib cage or abdomen ventilation using the respective value for %RC, as in the study of Tusiewicz, Bryan and Froese [2]. Linear regression lines were then calculated for

each component against $P_{E'}\text{CO}_2$. The mean slope for all subjects was found and plotted between points representing the mean compartmental minute volume and $P_{E'}\text{CO}_2$ at the beginning and end of the rebreathing runs. From data provided in Tusiewicz's study, we have plotted also the mean compartmental ventilation lines for her subjects between arbitrary points of 6.5 and 8 kPa on the X-axis.

(2) The tidal volumes were normalized for body weight and expressed as ml kg^{-1} , as in the study of Bickler, Dueck and Prutow [4]. These data were converted to rib cage and abdomen components and lines plotted as for (1). Similarly, we have plotted equivalent compartmental response lines for Bickler's subjects alongside ours, between 6.5 and 8.5 kPa.

Comparisons between awake and anaesthetized data were by paired Student's t test, except for the ventilatory response slopes. These data have been described previously as differing from a normal distribution [10], and our data did so significantly (by Shapiro–Francis W' test), so were compared using Wilcoxon's signed rank test.

RESULTS

One subject was excluded from the analysis because of an abnormal RIP trace during anaesthesia, showing a phase difference between the rib cage and abdomen signals. This subject is discussed below, and in all other subjects the peaks of the RIP signals were in phase.

The remaining 15 patients had mean age 28.2 yr, body mass index 23.7, FVC 4.3 litre and FEV₁ 3.9 litre (table I). Mean (SD) resting ventilation awake was 8.1 (2.2) litre min^{-1} at $P_{E'}\text{CO}_2$ 5.39 (0.36) kPa and, after maintenance of 1 MAC of isoflurane for 10 min, 6.0 (1.1) litre min^{-1} with $P_{E'}\text{CO}_2$ 6.29 (0.75) kPa (fig. 2). The mean %RC contribution to quiet breathing awake was 33 (15)% with a large scatter range (range 16–57%); during anaesthesia the mean was 39 (12)% (range 22–55%) (ns) (fig. 3).

The ventilatory response to carbon dioxide was significantly depressed during anaesthesia (fig. 2), the mean slope decreasing from 14.2 litre min^{-1} kPa^{-1} awake to 3.6 litre min^{-1} kPa^{-1} during anaesthesia ($P < 0.001$). The intercepts of the response lines were also decreased significantly, from a mean of 5.8 kPa awake to 4.8 kPa anaesthetized ($P < 0.02$).

Despite a wide scatter, the mean (SD) slopes of

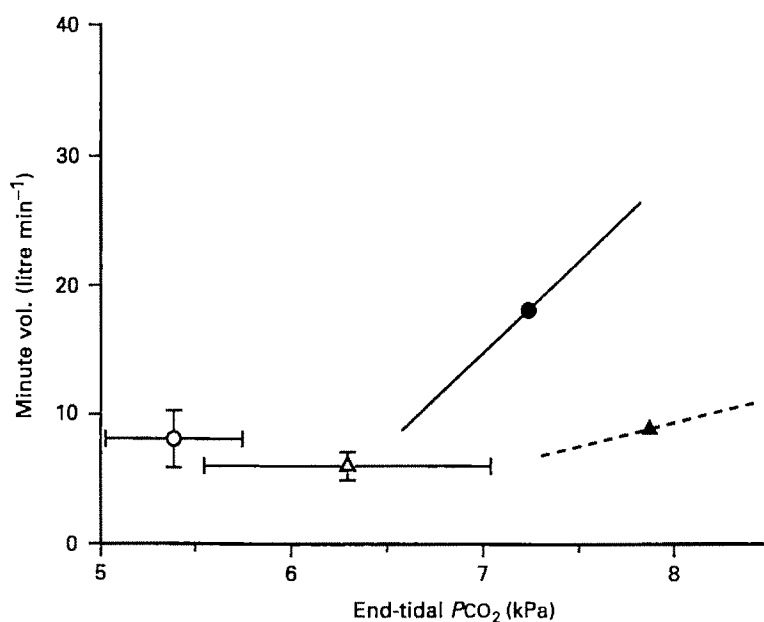


FIG. 2. Mean (SD) carbon dioxide response lines (● = awake; ▲ = isoflurane 1 MAC) and resting ventilation (○ = awake; △ = isoflurane 1 MAC).

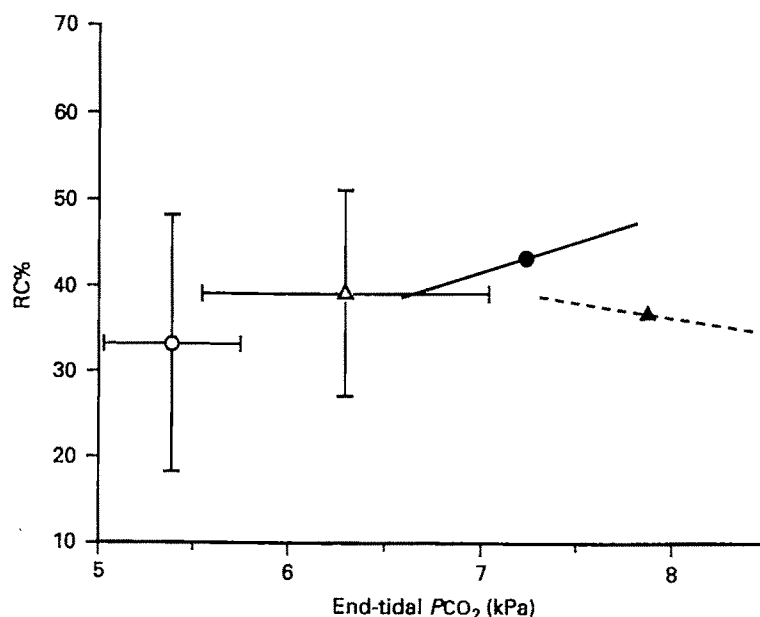


FIG. 3. Mean (SD) rib cage contribution (RC%) to resting (open symbols) and carbon dioxide stimulated ventilation. ●, ○ = Awake; ▲, △ = isoflurane 1 MAC.

$\Delta \% RC / \Delta P_{E'CO_2}$ (fig. 3) decreased significantly, from 7.1 (12.5)% kPa^{-1} awake to -3.6 (7.4)% kPa^{-1} during anaesthesia ($P < 0.05$). The slopes for awake subjects differed significantly from zero ($P < 0.05$), but slopes from anaesthetized subjects did not.

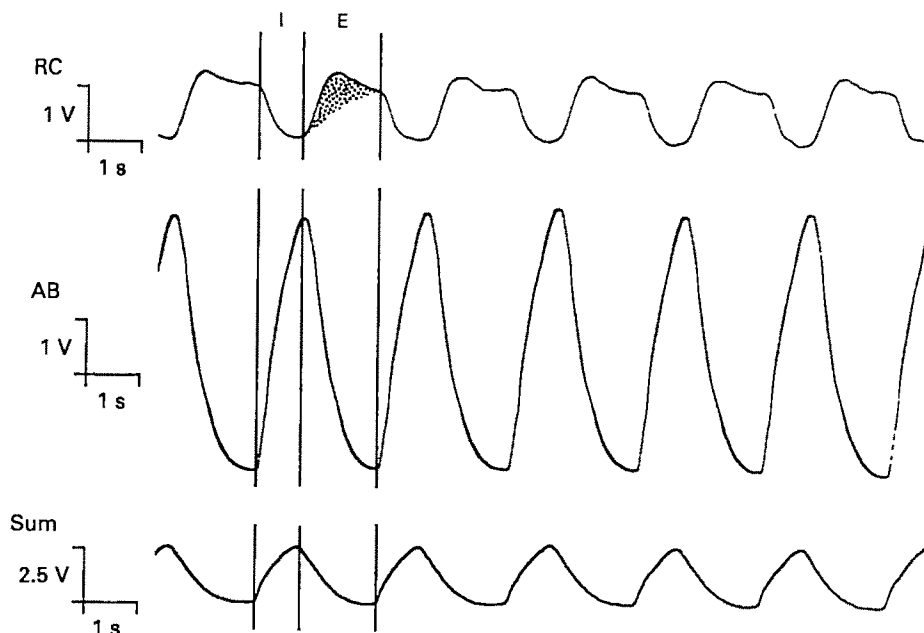


FIG. 4. Respiratory inductive plethysmography signals from excluded subject. I = Inspiration; E = expiration; RC = rib cage; AB = abdomen; Sum = electrical sum of RC and AB. Dotted area indicates expected line for a passive expiration. (Note: gain is reduced 2.5 times for sum signal.)

DISCUSSION

The anaesthetic technique used for this study was designed to reflect modern day-case clinical practice whilst providing 1 MAC of anaesthesia with a single volatile agent. In these patients, it is unlikely that the propofol was still contributing appreciably to anaesthesia at the time of the study (15 min after induction) [11]. For any study of respiratory mechanics during anaesthesia, an unobstructed airway is mandatory and a laryngeal mask provides this at lighter planes of anaesthesia than has been possible previously with tracheal intubation.

The subject who was excluded developed an abnormal RIP pattern of non-stimulated ventilation during anaesthesia, despite a clinically clear airway (fig. 4). The abdomen motion appears normal and predominant, but causes indrawing of the upper rib cage during inspiration, presumably representing abolished intercostal muscle tone. During expiration, the rib cage rapidly returns to normal, and even expands slightly. This may result either from activity of the intercostal/accessory muscles during expiration or, more likely, from active expiration by the abdominal muscles passively expanding the rib cage. This

pattern has been described in other studies (see below), but occurred in only one of our 16 subjects.

Non-stimulated ventilation

We have found no significant change in the %RC contribution to non-stimulated ventilation at 1 MAC of isoflurane anaesthesia. Tusiewicz, Bryan and Froese [2] and Jones and colleagues [3] both reported profound depression of the rib cage contribution to spontaneous ventilation during halothane anaesthesia. There are several possible explanations for this conflict with our results:

Methodology. Our study measured cross-sectional areas rather than circumference or antero-posterior diameter. These methods agree well in physiological studies [12], although in the study by Jones and colleagues [3] (using circumference measurements) the resting %RC of 14% is less than 50% that in most other studies of supine subjects. Methodology of rib cage-abdomen partitioning may therefore have contributed to differences in results between these studies, particularly that of Jones' group.

All body surface measurements of rib cage and abdomen do not necessarily reflect activity of the

intercostal and diaphragmatic muscles. For example, contraction of the diaphragm may cause expansion of the lower rib cage and activity of abdominal wall muscles will alter all dimensions of the abdominal cavity. Studies of the EMG of these muscle groups have been performed [13, 14], but we know of no study which has related EMG activity to body surface motion. Without EMG it is impossible to assess the activity of expiratory muscles in our subjects, or its subsequent effect on upper rib cage motion.

Airway. Preliminary studies in awake subjects indicated that the resistance to breathing between laryngeal masks and tracheal tubes is similar [15]. It is possible that differences in airway resistance, despite a clinically adequate airway, may result in various degrees of resistive loading and so alter %RC. This is clearly impossible to elucidate without measuring airway resistance through a laryngeal mask during anaesthesia, but the magnitude of the change in resistance in patients with adequate airways is unlikely to explain our findings. A study of methohexitone anaesthesia used two groups, with either intubation or facemask for airway maintenance. Despite a finding of different functional residual capacity with the differing airways, no comment was made on the %RC between the two groups [4]. It has been suggested that a tracheal tube may stimulate receptors in the airway, causing a reflex change in pulmonary mechanics, for instance bronchoconstriction [16], although it is not known if this reflex alters chest wall motion.

Use of suxamethonium. In the studies by Tusiewicz, Bryan and Froese [2] and Jones and colleagues [3], the majority of subjects were given suxamethonium to facilitate tracheal intubation. Their results may therefore represent a selective reduction in intercostal activity after suxamethonium, although this seems unlikely as 90 min elapsed between induction and study in Tusiewicz's subjects.

Specific respiratory effects of different anaesthetic agents. Respiratory depression at 1 MAC of isoflurane is well known [17]; our subjects' resting minute volumes decreased by 2 litre min^{-1} with a consequent increase in $P_{\text{E}'\text{CO}_2}$ of 0.9 kPa. The size of V_T has been shown to affect %RC. Voluntarily increasing V_T in awake supine volunteers increased the %RC in the majority of subjects [18],

but we know of no studies of involuntary changes in V_T or the effects of decreasing V_T . As increasing V_T results in increased %RC, it is likely that decreasing V_T would reduce the %RC, which is the opposite of our findings. Also, taking potency into account, isoflurane does not differ greatly from halothane in its ventilatory effects, causing a similar reduction in V_T with less increase in ventilatory frequency [19]. Changes in V_T are therefore unlikely to account for the difference in our observations from those with halothane [2, 3].

There are other circumstances during anaesthesia in which %RC has been maintained or even increased. It is agreed that paralysis and IPPV cause an increase in rib cage contribution, regardless of the other agents used [3, 20], so only spontaneous ventilation is discussed further. Methohexitone bolus followed by infusion caused no change in %RC [4], whilst a similar regimen of ketamine resulted in a significant increase in rib cage contribution [5]. Sedation with either midazolam or diazepam also increased rib cage contribution to ventilation, by 15–20% [6, 7]. Pethidine administered during midazolam sedation also caused an increase in %RC, this effect being antagonized by naloxone [6]. The benzodiazepines and volatile agents used in all these studies cause similar degrees of overall respiratory depression, reducing V_T to approximately 40% of control so, as discussed above, the varied effects on %RC cannot be ascribed simply to changes in V_T .

It is clear, therefore, that different agents and doses do have variable effects on the rib cage and abdomen components of the respiratory system. However, it remains unclear as to how this occurs, and where the effect is mediated between the medullary respiratory centre and the muscle fibre.

Depth of anaesthesia. Our study was undertaken at a lighter level of anaesthesia than those of Tusiewicz, Bryan and Froese [2] or Jones and colleagues [3]. Tusiewicz's study was performed at 1.4 MAC of halothane in oxygen, whilst Jones' study used between 0.83 and 3.3 MAC halothane in addition to nitrous oxide. Presumably this involved at least 50% nitrous oxide, providing a minimum total of 1.33 MAC. Jones' group also demonstrated that progressive rib cage depression occurred with increasing anaesthetic concentration. A previous preliminary report of a study of isoflurane and rib cage motion showed no significant change in rib cage contribution up to

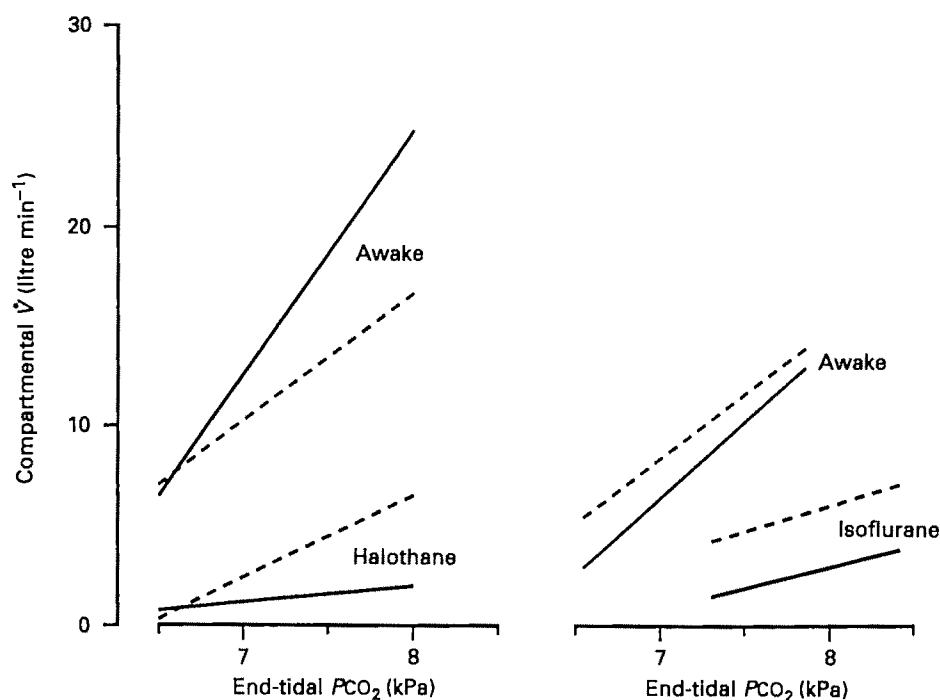


FIG. 5. Comparison of our results (right side) with those of Tusiewicz, Bryan and Froese [2] (left side). $\dot{V}$ = expired minute volume. — = Rib cage; --- = abdomen.

1.5 MAC, although the %RC did decrease by 15% at this value [21]. This study also demonstrated that airway obstruction during anaesthesia caused instability of the lower rib cage. We saw no evidence of this in the high rib cage recordings in our study, except in the excluded subject who showed similar rib cage instability at nipple level with a clear airway. It seems very likely that the most important difference between our findings and those of Tusiewicz, Jones and their colleagues is the greater depth of anaesthesia used to allow tolerance of the tracheal tube during inhalation anaesthesia with spontaneous breathing—a problem we have avoided by use of a laryngeal mask.

Carbon dioxide stimulated ventilation

Slopes of ventilatory response to carbon dioxide were reduced to about 25% of the awake value (fig. 2), which is similar to results in other studies [17, 19]. We have found a small, but significant, increase of $7.1\% \text{ kPa}^{-1}$ in the rib cage contribution to ventilation during carbon dioxide rebreathing whilst awake. This rib cage "recruitment" has been demonstrated previously in conscious subjects, and is particularly marked in subjects who

have large increases in tidal volume [22]. In the present study, this rib cage recruitment was abolished by anaesthesia, which at 1 MAC resulted in a negative $\Delta\% \text{ RC} / \Delta P_{\text{E}'\text{CO}_2}$ slope not significantly different from zero (fig. 3). Absolute rib cage ventilation continued to increase with PCO_2 but the slope of the rib cage component of minute volume was greatly reduced (fig. 5). Tusiewicz, Bryan and Froese [2] previously demonstrated profoundly decreased rib cage motion during carbon dioxide rebreathing at 1.4 MAC halothane anaesthesia, and concluded that a major part of the ventilatory depression seen with halothane resulted from suppression of intercostal muscle activity. However, these observations were illustrated (in their fig. 5) by total abolition of rib cage response to carbon dioxide in one subject, who was aged only 9 yr and not necessarily representative of the general adult population. From our figure 5, it can be seen that even when our results are processed in the same way, and using the mean of Tusiewicz's five subjects, there is more pronounced depression of rib cage contribution in those subjects than ours. We believe this again results from deeper anaesthesia in the subjects studied by Tusiewicz's

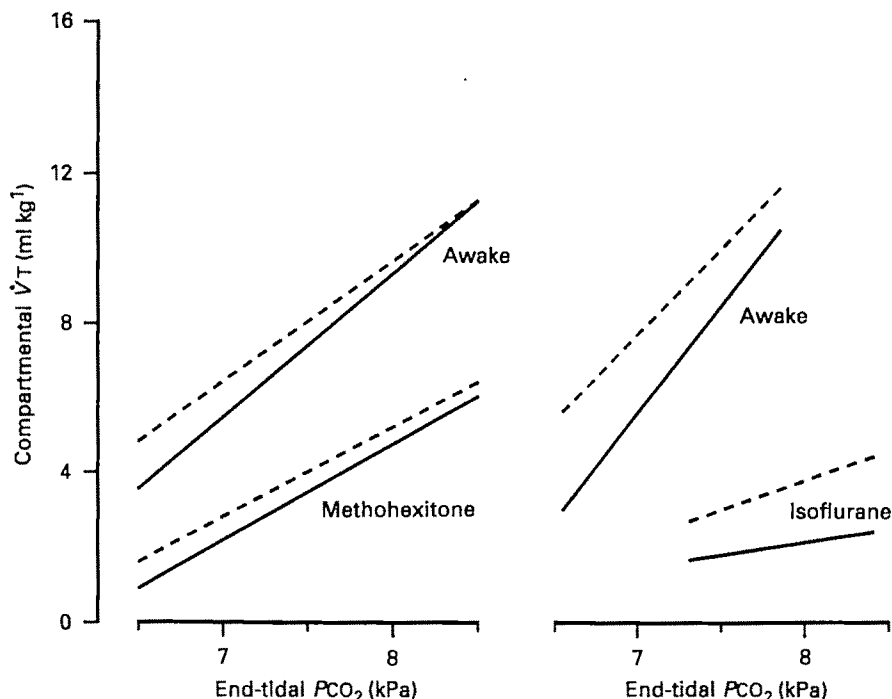


FIG. 6. Comparison of our results (right side) with those of Bickler, Dueck and Prutow [4] (left side). $\dot{V}_T$ = Tidal volume. — = Rib cage; --- = abdomen.

group. Our results for compartmental tidal volumes are very similar to those of Bickler (methohexitone anaesthesia), our subjects displaying, if anything, greater depression of the rib cage (fig. 6). Equivalence of the depth of anaesthesia between inhalation and i.v. agents is difficult to assess, and it is possible that Bickler did not achieve a depth of anaesthesia equivalent to 1 MAC as in our study.

In conclusion, we have shown that at 1 MAC of isoflurane, selective depression of rib cage motion is undetectable without the severe provocation of carbon dioxide rebreathing. There is at present no evidence that any currently used anaesthetic agent other than halothane can cause significant depression of rib cage motion during ventilation without carbon dioxide stimulation. Thus most modern inhalation anaesthetic agents at 1 MAC should not compromise patients with poor ventilatory muscle function, even when breathing spontaneously. Compared with the awake state, anaesthesia causes a reduction in the relative contribution of the rib cage to carbon dioxide stimulated ventilation, but both rib cage and abdomen compartments continue to contribute,

although at a reduced level, and depression of the overall ventilatory response to carbon dioxide cannot be ascribed solely to the rib cage.

REFERENCES

1. Snow J. *On Chloroform and Other Anaesthetics: Their Action and Administration*. London: Churchill, 1858; 90.
2. Tusiewicz K, Bryan AC, Froese AB. Contributions of changing rib cage-diaphragm interactions to the ventilatory depression of halothane anaesthesia. *Anesthesiology* 1977; 47: 327-337.
3. Jones JG, Faithfull D, Jordan C, Minty B. Rib cage movement during halothane anaesthesia in man. *British Journal of Anaesthesia* 1979; 51: 399-407.
4. Bickler PE, Dueck R, Prutow RJ. Effects of barbiturate anaesthesia on functional residual capacity and ribcage/diaphragm contributions to ventilation. *Anesthesiology* 1987; 66: 147-152.
5. Mankikian B, Cantineau JP, Sartene R, Clergue F, Viars P. Ventilatory pattern and chest wall mechanics during ketamine anaesthesia in humans. *Anesthesiology* 1986; 65: 492-499.
6. Berggren L, Eriksson I, Mollenholt P. Changes in breathing pattern and chest wall mechanics after benzodiazepines in combination with meperidine. *Acta Anaesthesiologica Scandinavica* 1987; 31: 381-386.
7. Morel DR, Forster A, Bachmann M, Suter PM. Effect of intravenous midazolam on breathing pattern and chest wall mechanics in humans. *Journal of Applied Physiology*:

- Respiratory, Environmental, and Exercise Physiology* 1984; 57: 1104-1110.
8. Read DJC. A clinical method for assessing the ventilatory response to carbon dioxide. *Australasian Annals of Medicine* 1967; 16: 20-32.
 9. Chadha TS, Watson H, Birch S, Jenouri GA, Schneider AW, Cohn MA, Sackner MA. Validation of respiratory inductive plethysmography using different calibration procedures. *American Review of Respiratory Diseases* 1982; 125: 644-649.
 10. Rebuck AS, Slutsky AS. Measurement of ventilatory responses to hypercapnia and hypoxia. In: Hornbein TF, ed. *Regulation of Breathing, Part 2. Lung Biology and Health Diseases Serial*, Vol. 17, Part II. New York: Dekker, 1981; 745-772.
 11. Logan MR, Duggan JE, Levack ID, Spence AA. Single-shot anaesthesia for outpatient dental surgery. *British Journal of Anaesthesia* 1987; 59: 179-183.
 12. McCool FD, Kelly KB, Loring SH, Greaves IA, Mead J. Estimates of ventilation from body surface measurements in unrestrained subjects. *Journal of Applied Physiology* 1986; 61: 1114-1119.
 13. Kaul SU, Heath JR, Nunn JF. Factors influencing the development of expiratory muscle activity during anaesthesia. *British Journal of Anaesthesia* 1973; 45: 1013-1018.
 14. Takasaki Y, Orr D, Popkin J, Ailiang X, Bradley TD. Effect of hypercapnia and hypoxia on respiratory muscle activation in humans. *Journal of Applied Physiology* 1989; 67: 1776-1784.
 15. Ferguson C, Herdman M, Evans K, Hayes M, Davies R, Cole PV. Flow resistance of the laryngeal mask. *British Journal of Anaesthesia* 1991; 66: 400P.
 16. Dueck R. Pulmonary effects of tracheal intubation. *Proceedings of the 8th European Congress of Anesthesiology*, Warsaw 1990. (In Press.)
 17. Knill RL, Kieraszewicz HT, Dodgson BG, Clement JL. Chemical regulation of ventilation during isoflurane sedation and anaesthesia in humans. *Canadian Anaesthetists Society Journal* 1983; 30: 607-614.
 18. Sharp JT, Goldberg NB, Druz WS, Danon J. Relative contributions of rib cage and abdomen to breathing in normal subjects. *Journal of Applied Physiology* 1975; 39: 608-618.
 19. Fourcade HE, Stevens WC, Larson CP, Cromwell TH, Bahlman SH, Hickey RF, Halsey MJ, Eger EI. The ventilatory effects of Forane, a new inhaled anesthetic. *Anesthesiology* 1971; 35: 26-31.
 20. Hedenstierna G, Lofstrom B, Lundh R. Thoracic gas volumes and chest-abdomen dimensions during anaesthesia and muscle paralysis. *Anesthesiology* 1981; 55: 499-506.
 21. Cantineau JP, Mankikian B, Poete P, Sartene R, Clergue F, Viars P. Ventilatory pattern and chest wall mechanics during isoflurane anaesthesia. *Anesthesiology* 1985; 63: A551.
 22. Lumb AB, Nunn JF. Ribcage contribution to CO₂ response during rebreathing and steady state methods. *Respiration Physiology* 1991; 85: 97-110.

SCREENING FOR ANTIBODIES ASSOCIATED WITH HALOTHANE HEPATITIS

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SUMMARY

The diagnosis of halothane hepatitis (HH) may be assisted by detection of antibodies reacting to trifluoroacetylated proteins (anti-TFA antibodies). An enzyme-linked immunosorbent assay (ELISA) utilizing trifluoroacetylated rabbit serum albumin (TFA-RSA) as antigen detected anti-TFA antibodies in 67% of sera from patients for whom a clinical diagnosis of HH was made. Anti-TFA antibodies were detected in 33% of sera when using an ELISA with liver microsomal protein from halothane-treated rabbits as antigen. Absorption of the sera with untreated rabbit liver microsomal protein before using the microsomal protein ELISA resulted in detection of anti-TFA antibodies in 42% of sera. Using the presumptive hapten N-ε-trifluoroacetyl-L-lysine to block antibody binding in an ELISA resulted in positive detection in 50% of sera: the results did not always agree with the other ELISA methods. The TFA-RSA ELISA was the most sensitive method and, combined with the TFA-lysine blocking ELISA, resulted in 92% of sera from HH patients testing positive for HH-associated antibodies.

KEY WORDS

Anaesthetics, volatile: halothane. Complications: halothane hepatitis. Immune response: anti-TFA antibodies.

Two types of hepatotoxic reaction may result from use of the inhalation anaesthetic halothane. A mild form of hepatotoxicity occurs in about 20% of patients receiving halothane anaesthesia [1]. The most remarkable finding is an increase to greater than normal serum concentrations of liver enzymes, especially alanine aminotransferase. This phenomenon has been reproduced in rats [2] and guineapigs [3, 4]. A much rarer and more severe consequence of halothane anaesthesia, halothane hepatitis (HH), is seen about once in

35000 uses [5]. HH does not appear to be a particularly severe form of direct halothane toxicity; in contrast, it appears to be a fundamentally different disease [6].

Typically, HH begins to manifest about 5 days after anaesthesia [7], when the patient develops a rapid increase in serum concentrations of transaminase and bilirubin [8, 9]. Other signs, not always seen, include blood and liver eosinophilia, circulating immune complexes and massive hepatic centrilobular necrosis [10, 11].

The most generally accepted theory is that HH is an immunological disease similar in fundamental aspects to other drug hypersensitivity reactions. Halothane is metabolized to several metabolites that can bind readily to cellular macromolecules [12]. One particular metabolite, the acid chloride product of hepatic oxidative biotransformation, appears to bind to free amino groups in proteins, thus forming hapten-protein complexes [13, 14]. These complexes appear, in rare instances, to induce an immune response resulting in the production of antibodies, T-cells, or both, which recognize this hapten. When a secondary exposure to halothane occurs, the immune system responds to the production of these hapten-protein complexes by mounting an immune response to the patient's liver, resulting in an autoimmune form of hepatitis. Although the exact nature of the immunogen(s) is not known, there appear to be two general classes of antibodies produced in HH: hapten-specific antibodies and antibodies induced by the binding of hapten to carrier proteins which are directed against liver

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protein epitopes [15, 16]. Indeed, the generalization of the immune response from hapten-specific antibodies (and T-cells) to autoimmune antibodies (and T-cells) could be the immunological basis of the disease.

Diagnosis of HH is difficult and generally is made by exclusion of other aetiological factors. Some patients appear to be at risk of developing HH: obese, middle-aged females who have been exposed previously to halothane are at greatest risk [8]. Repeated exposure to halothane appears to be an independent risk factor, providing further evidence for the immunological basis of the disease [17].

There is no generally accepted laboratory method for establishing a diagnosis of HH. In this study, we have examined currently used laboratory methods and have evaluated the usefulness of these procedures.

METHODS

Patient samples

Serum samples, referred to this laboratory by physicians at various hospitals, were obtained from patients for whom a diagnosis of halothane hepatitis was made on clinical grounds. Patients typically developed jaundice, increased serum concentrations of liver enzymes, and other signs of hepatitis after halothane anaesthesia. Three samples were obtained from male patients (one a 22-month old infant); two patients died of hepatitis. Two patients developed hepatitis after isoflurane anaesthesia. In two cases, sera were obtained from health workers (one operating room nurse and one anaesthetist) presenting with hepatitis after repeated occupational exposure to halogenated anaesthetics.

In most cases, other potential causes of hepatitis (hepatitis A, hepatitis B, cytomegalovirus, and Epstein-Barr virus) were reported to have been excluded on laboratory analysis. In addition, sera were tested for hepatitis B surface antigen (Ausria II-125, Abbott Laboratories, North Chicago, IL) and for antibody to hepatitis C virus (Hepatitis C EIA, Abbott Laboratories).

Two groups of randomly selected patient control sera were used: the first group contained samples from seven patients with increased serum concentrations of liver enzyme and the second group contained 10 patients with normal serum concentrations of liver enzyme. None of the controls had been exposed to halothane and none

had been diagnosed with either primary biliary cirrhosis or chronic active hepatitis—both diseases known to give false positive results in immunoassays for HH-associated antibodies [18, 19].

Preparation of TFA-RSA

Trifluoroacetylated rabbit serum albumin (TFA-RSA) was prepared according to the method of Goldberger and Anfinsen [20]. Rabbit serum albumin fraction V (RSA; United States Biochemical Corp., Cleveland, OH) was reacted with S-ethylthioltrifluoroacetate (Chemical Dynamics Corp., South Plainfield, NJ). The product was dialysed with water for 3 days, then collected and lyophilized. Trifluoroacetylation was confirmed by measuring the bound fluorine content of the product [21].

Preparation of rabbit microsomal proteins

Two New Zealand male white rabbits (1.5–2 kg each) were obtained from Viera and Sons Rabbitry, Maricopa, AZ. One rabbit was exposed to 1% halothane in a 95% oxygen atmosphere for 45 min. The rabbit was allowed to recover and was killed 18 h later. The second rabbit was used as an unexposed control. After both animals were killed, the livers were removed and microsomal proteins were isolated by differential centrifugation [22]. Trifluoroacetylation of the microsomal proteins was confirmed by ELISA using rabbit anti-trifluoroacetylated albumin antiserum, prepared as described by Callis and others [23].

TFA-RSA ELISA

Serum samples were initially tested for anti-halothane antibody by the ELISA method of Callis and others [23]. Microtitre plates (Sero-cluster half well plates; COSTAR, Cambridge, MA) were coated with either TFA-RSA or RSA (1 µg per well in phosphate-buffered saline (PBS), pH 7.4) by overnight incubation at 4 °C. After washing with 0.05% (v/v) Tween 20 (Sigma) in PBS (PBS-Tween), non-specific binding sites were blocked by incubating the plates with 3% (w/v) gelatin (J. T. Baker, Phillipsburg, PA) in PBS (gelatin-PBS) for 1 h at 37 °C. The plates were washed with PBS-Tween and serial dilutions of patient serum in gelatin-PBS added, followed by incubation at room temperature for 1 h. Bound antibody was detected by incubating the plates with goat anti-human IgG-peroxidase conjugate (Organon Teknika-Cappel, Malvern,

PA), diluted 1:1000 in gelatin-PBS, for 1 h at room temperature, followed by development with the peroxidase substrate 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid) (ABTS; Sigma). The reaction was stopped with a 5% (w/v) aqueous solution of sodium dodecyl sulphate (Sigma) and the plates were read on a Skatron EAR 340 microtitre plate reader (Skatron, Sterling, VA) with a 405-nm filter.

Halothane microsome ELISA

Serum samples were assayed by an adaptation of the method of Kenna, Neuberger and Williams [24]. Microtitre plates (PETG Fastbinder plates; COSTAR) were coated with either halothane-treated rabbit microsomal protein or normal rabbit microsomal protein by incubating protein 1.5 µg per well in PBS, pH 7.4, overnight at 4 °C. A solution of 0.5% (w/v) casein (Sigma) and 0.01% (w/v) thimerosol (Sigma) in Tris-buffered saline 10 mmol litre⁻¹, pH 7.6 (casein-Tris buffer) was used to wash the plate and block non-specific binding sites [25]. Serum samples were diluted in casein-Tris buffer, added to the plates, and incubated for 1 h at 37 °C. After washing, the plates were incubated with goat anti-human IgG-peroxidase conjugate (Organon Teknika-Cappel), diluted 1:1000 in casein-Tris buffer, for 3 h at room temperature. The plates were washed and developed with a solution of o-phenylenediamine in citrate-phosphate buffer. The plates were stopped with a dilute solution of hydrofluoric acid and read on a Skatron EAR 340 plate reader using a 450-nm filter.

Absorption with normal rabbit microsomes

In order to reduce the immunoreactivity of patients' sera with normal rabbit microsomal protein, an absorption procedure was used. Patient serum was mixed with normal rabbit microsomal protein diluted in casein-thimerosol buffer, incubated for 90 min at room temperature, and centrifuged at 105 000 *g* for 2 h. The supernatant fraction was removed and absorbed again by the same procedure. The final supernatant fraction was then tested in the halothane microsome ELISA.

TFA-lysine blocking ELISA

The ability of N-ε-trifluoroacetyl-L-lysine (TFA-lysine), the presumptive hapten formed by the reaction of oxidative metabolites of halothane with self protein, to block the binding of anti-

bodies from HH patients to microsomal protein from halothane-treated rabbits was measured by a modified ELISA. Patient serum was diluted with a solution of TFA-lysine (Chemical Dynamics Corp., South Plainfield, NJ) in casein-thimerosol buffer to yield a final hapten concentration of 100 mmol litre⁻¹. The dilutions were incubated overnight at 4 °C followed by centrifugation at 105 000 *g* for 2 h. The supernatant fraction was tested for reactivity with halothane-treated rabbit microsomes as described above. The data were expressed as the pre-blocking absorbance minus the post-blocking absorbance.

Statistical analysis

For all ELISA results, corrected absorbance values were considered to be positive for anti-halothane metabolite antibody activity if they were greater than the sum of the mean of the absorbance values for controls plus 2 SD of the mean. To test for statistical significance, absorbance values of patient and control groups were compared by analysis of variance (ANOVA).

RESULTS

For initial evaluation, all the serum samples were tested using the TFA-RSA ELISA (fig. 1). Serum samples which gave an absorbance of greater than 0.81 for a 1:100 dilution were considered to be positive for specific anti-halothane metabolite antibody activity. Using this criterion, eight of 12

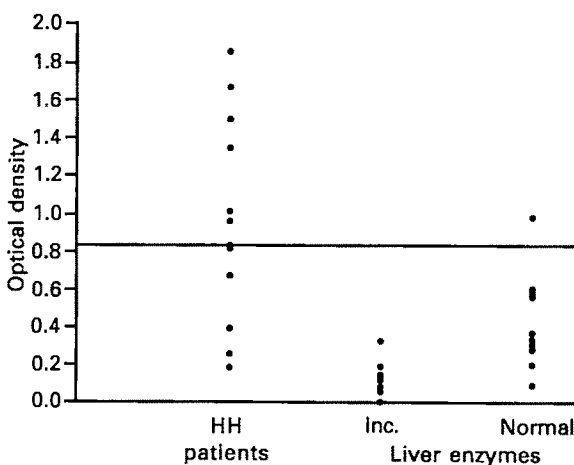


FIG. 1. ELISA (405-nm filter) using trifluoroacetylated rabbit serum albumin as antigen. The horizontal line at optical density 0.810 (the mean of controls plus 2 SD of the mean) indicates the cut-off used to determine positivity.

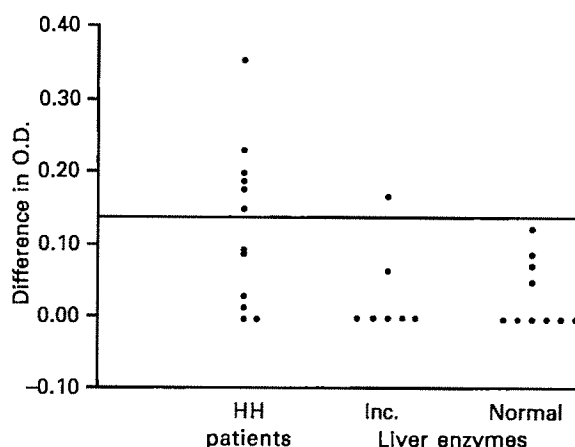
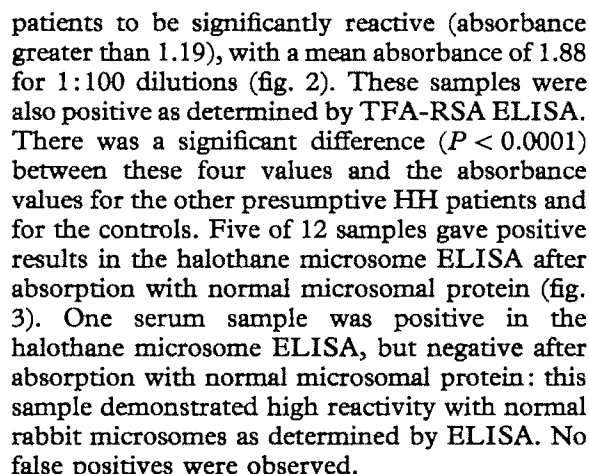


FIG. 4. Halothane-treated rabbit microsome ELISA using TFA-lysine to block antibody binding (TFA-lysine blocking ELISA). The difference in optical density (O.D.) was determined by subtracting the O.D. of the ELISA after TFA-lysine blocking from the O.D. determined without TFA-lysine blocking. An O.D. difference of 0.140 (mean of controls + 2 SD) was used to determine positivity.



In the TFA-lysine blocking ELISA, some inhibition of antibody binding to halothane-modified rabbit microsomal protein could be demonstrated for six of 12 HH serum samples (fig. 4). Three samples were positive in the TFA-lysine blocking ELISA, but were negative in the other immunoassays. One sample (from patient No. 2), which was positive in all immunoassays except the TFA-lysine blocking ELISA, was positive for anti-hepatitis C antibody. All other samples were negative for hepatitis B surface antigen and anti-hepatitis C antibody. Of particular interest are results of the isoflurane-related and occupational exposure cases. Serum from one

Use of the halothane microsome ELISA demonstrated four of 12 serum samples from HH

isoflurane-related case (patient No. 10) was positive for antibody in both the TFA-RSA ELISA and the halothane microsome ELISA after absorption with normal microsomal protein. A pretreatment serum sample was available and tested negative in both assays. Serum from one occupational exposure case (patient No. 11) was also positive for antibody in both the TFA-RSA and postabsorption halothane microsome ELISA.

DISCUSSION

As part of our research into the mechanisms of HH, we receive sera by passive referral. Although our primary interest is research, we also have a role in patient care. We consider a sensitive assay for HH-associated antibody to be more important than a specific assay. Thus a certain percentage of false positive results should be more acceptable than the possibility of false negative results. As alternatives to halothane may be used, if a patient tests falsely positive for HH-associated antibody, the patient should not suffer. On the other hand, if a false negative result is reported a patient may be exposed unnecessarily to a potentially deadly agent.

The TFA-RSA ELISA used in this study is based on the method first reported by Satoh and others [26]. An evaluation of this basic technique demonstrated that 59% of 44 diagnosed HH patients had serum antibodies detectable by this method [18]. Although no normal controls or patients who had received multiple halothane exposures without symptoms of hepatic dysfunction were reactive in this assay, 17% of 17 primary biliary cirrhosis patients and 46% of 13 chronic active hepatitis patients had serum samples that were reactive. Thus, for at least two groups of patients, there was the possibility of a false positive result by this method. Evaluation of the assay by Hubbard and others [27] demonstrated that serum samples from five of six patients with apparent HH were immunoreactive in the TFA-RSA ELISA. Ten patients exposed to halothane but without symptoms of HH were essentially non-reactive in this assay.

Two recent studies examined the efficacy of the TFA-RSA ELISA. Martin, Kenna and Pohl [19] reported that 26 of 44 serum samples (59%) from presumptive HH patients tested positive using this assay and 15 of 126 patient control samples gave apparently false positive results (12%). Bird and Williams [28] reported 12 of 40 HH serum

samples (30%) were positive and none of the patient control samples gave false positive results. There are several possible reasons for the apparent differences in these findings. Presumably the patient populations tested were different. Although the size of the control groups were different, both studies included patients with similar diagnoses. Although Martin and others [18, 19] reported a high false positive rate for patients with primary biliary cirrhosis or chronic active hepatitis, no false positives for patients with one of these diseases was observed by Bird and Williams.

Small differences in assay procedures could also account for variations in results. Bird and Williams [28] diluted serum samples 1:50 and incubated for 3 h at room temperature, followed by detection of bound antibody by incubation with a 1:1000 dilution of peroxidase-labelled second antibody, for 1 h at room temperature. Martin, Kenna and Pohl [19] incubated serum samples (1:100) for 2 h at room temperature, followed by incubation with the labelled second antibody (diluted 1:500) for 3 h at room temperature. The longer incubation and lower dilution of labelled second antibody used by Martin, Kenna and Pohl may have resulted in higher non-specific binding and thus a greater possibility of false positives. Examination of the results reported by Martin, Kenna and Pohl shows that, with one exception (a serum sample from a primary biliary cirrhosis patient), all of the false positive results were in the low absorbance range (optical density (O.D.) apparently less than 0.5). Bird and Williams found a significant relationship between detection of antibody and severity of disease, with 75% of patients demonstrating encephalopathy testing positive for anti-halothane metabolite antibody. This relationship was not reported by Martin, Kenna and Pohl.

Martin, Kenna and Pohl [19] reported five false negative results. There was no way of assessing the incidence of false negative results in the study by Bird and Williams [28]. We found no false negative results using the TFA-RSA ELISA with the halothane microsome ELISA as the basis for confirmation (table I). Our method for evaluating ELISA data differed from other reports: we considered an ELISA absorbance value to be positive if it was greater than the mean of control values plus 2 sd of the mean: other authors use 3 sd. Thus we use a method of data evaluation that allows for the greater possibility of a false

TABLE I. Comparison of analyses for halothane-induced antibodies in patients diagnosed with halothane hepatitis. *ELISA using halothane-treated rabbit microsomal protein as antigen (halothane microsome ELISA). †ELISA using halothane-treated rabbit microsomal protein with sera pre-absorbed with untreated rabbit microsomal protein. ‡TFA-lysine blocking ELISA

Patient No.	TFA-RSA ELISA	Halothane microsomes*	Pre-absorbed microsomes†	TFA-lysine blocking‡
1	—	—	—	+
2	+	+	+	—
3	+	—	—	—
4	+	—	—	—
5	—	—	—	+
6	+	+	+	+
7	+	+	—	+
8	—	—	—	+
9	+	+	+	+
10	+	—	+	—
11	+	—	+	—
12	—	—	—	—

positive in the belief that it is preferable to err on the side of caution.

In agreement with both Martin, Kenna and Pohl [19] and Bird and Williams [28], we found two samples with high anti-RSA activity, one a presumptive HH patient and the other from the increased liver enzyme group. For the HH sample, subtracting the anti-RSA absorbance reduced the absorbance in the TFA-RSA ELISA to a non-significant value, which was also true for the control sample. Subsequent assays demonstrated that the control sample was negative for anti-halothane metabolite antibody activity.

The most striking result of the ELISA using halothane-treated rabbit microsomal protein as antigen was the lack of sensitivity of the assay compared with the TFA-RSA ELISA. Although four samples gave absorbance values that were significantly different from controls ($P < 0.0001$), eight of the HH samples did not differ significantly from controls. Pre-absorption with normal microsomal protein before testing with halothane-treated microsomal protein increased the sensitivity of the assay. Using 0.86 as the absorbance cutoff, five of 12 samples (42%) were positive. All were positive also in the TFA-RSA ELISA. There were no false positives.

The sensitivity of the halothane-treated microsome ELISA has been reported to be 67% [19], 67% [24] and 72% [29]. Although the sensitivity reported here is lower, this could reflect higher anti-microsomal antibody titres in the samples

tested. A basic premise of halothane hepatitis research is that, although the initial immune response is hapten-specific, this response broadens to a generalized autoimmune response to self proteins, especially to microsomal proteins [15]. Thus pre-absorption could remove antibodies with partial hapten, partial carrier protein specificity, reducing the sensitivity of the assay.

For the TFA-lysine blocking ELISA, six of 12 samples (50%) demonstrated binding inhibition, including three samples that were negative in all of the previous assays. One false positive was observed. The presence of low-titre antibodies that appear to be immunoreactive with TFA-lysine could be the result of delay in obtaining a serum sample or the consumption of antibodies in the pathological process.

To our knowledge, this is the first study in which sera from suspected HH patients were tested for anti-hepatitis C antibodies. One serum sample, from patient No. 2, which was positive in three of the immunoassays, tested positive for anti-hepatitis C virus. It is not known if the patient was diagnosed incorrectly for HH or had a concurrent hepatitis C infection.

One patient (No. 10) had received isoflurane before developing hepatitis. To our knowledge, this is the first report of serological markers for HH being detected in a suspected isoflurane-related hepatitis patient. As a pretreatment serum sample tested negative for HH-related antibodies, this patient indeed could have suffered from hepatitis related to isoflurane anaesthesia. Unfortunately, primary biliary cirrhosis or chronic active hepatitis were not excluded from the diagnosis, complicating interpretation of the results.

Serum from an operating room nurse (patient No. 11) occupationally exposed to halogenated volatile anaesthetics tested positive in both the TFA-RSA ELISA and the halothane microsome ELISA. Again, primary biliary cirrhosis or chronic active hepatitis did not appear to have been excluded from the diagnosis. Both the isoflurane-related hepatitis and occupationally-related hepatitis patients demonstrate a problem for a passive referral system: we can only report the results of our assays. The physician must establish the diagnosis based, not only on laboratory data, but also on other evidence.

Combining the results of two methods, the TFA-RSA ELISA and the TFA-lysine blocking ELISA, resulted in 92% of sera from presumptive

HH patients testing positive for HH-associated antibodies. In conclusion, a combination of the TFA-RSA ELISA and TFA-lysine blocking ELISA appears to be acceptable as a screening method for detection of antibodies associated with HH.

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REFERENCES

- Wright R, Chisholm M, Lloyd B, Edwards JC, Bade OE, Hawksley M, Moles TM, Gardner MJ. Controlled prospective study of the effect on liver function of multiple exposure to halothane. *Lancet* 1975; 1: 814-820.
- Brown BR, Sipes IG. Biotransformation and hepatotoxicity of halothane. *Biochemical Pharmacology* 1977; 26: 2091-2094.
- Hughes HG, Lang CM. Hepatic necrosis produced by repeated administration of halothane to guinea-pigs. *Anesthesiology* 1972; 36: 466-471.
- Lind RC, Gandolfi AJ, Brown BR, Hall PM. Halothane hepatotoxicity in guinea pigs. *Anesthesia and Analgesia* 1987; 66: 222-228.
- Stock JGL, Strunin L. Unexplained hepatitis following halothane. *Anesthesiology* 1985; 63: 424-439.
- Hubbard AK, Gandolfi AJ, Brown BR. Immunological basis of anesthetic-induced hepatotoxicity. *Anesthesiology* 1988; 69: 814-817.
- Neuberger J, Williams R. Halothane anaesthesia and liver damage. *British Medical Journal* 1984; 289: 1136-1139.
- Walton B, Simpson BR, Strunin L, Doniach D, Perrin J, Appleyard AJ. Unexplained hepatitis following halothane. *British Medical Journal* 1976; 1: 1171-1176.
- Neuberger J, Gimson AES, Davis M, Williams R. Specific serological markers in the diagnosis of fulminant hepatic failure associated with halothane anaesthesia. *British Journal of Anaesthesia* 1983; 55: 15-19.
- Canalese J, Wyke RJ, Vergani D, Eddleston ALWF, Williams R. Circulating immune complexes in patients with fulminant hepatic failure. *Gut* 1981; 22: 845-848.
- Neuberger J. Halothane hepatitis. *ISI Atlas of Science: Pharmacology*. Philadelphia: ISI, 1988; 309-313.
- Gandolfi AJ, White RD, Sipes IG, Pohl LR. Bioactivation and covalent binding of halothane *in vitro*: Studies with [³H]- and [¹⁴C]-halothane. *Journal of Pharmacology and Experimental Therapeutics* 1980; 214: 721-725.
- Satoh H, Fukuda Y, Anderson DK, Ferrans VJ, Gillette JR, Pohl LR. Immunological studies on the mechanism of halothane-induced hepatotoxicity: Immunohistochemical evidence of trifluoroacetylated hepatocytes. *Journal of Pharmacology and Experimental Therapeutics* 1985; 233: 857-862.
- Satoh H, Gillette JR, Davies HW, Schulick RD, Pohl LR. Immunochemical evidence of trifluoroacetylated cytochrome P-450 in the liver of halothane-treated rats. *Molecular Pharmacology* 1985; 28: 468-474.
- Pohl LR, Kenna JG, Satoh H, Christ D, Martin JL. Neoantigens associated with halothane hepatitis. *Drug Metabolism Reviews* 1989; 20: 203.
- Satoh H, Martin BM, Schulick AH, Christ DD, Kenna JG, Pohl LR. Human anti-endoplasmic reticulum antibodies in sera of patients with halothane-induced hepatitis are directed against a trifluoroacetylated carboxylesterase. *Proceedings of the National Academy of Science U.S.A.* 1989; 86: 322-326.
- Inman WHW, Mushin WW. Jaundice after repeated exposure to halothane: An analysis of reports to the Committee on Safety of Medicines. *British Medical Journal* 1974; 1: 5-10.
- Martin JL, Kenna JG, Satoh H, Pohl LR. Assays for the detection of antibodies directed against halothane-induced liver neoantigens in the sera of patients with halothane hepatitis. *Anesthesiology* 1988; 69: A439.
- Martin JL, Kenna JG, Pohl LR. Antibody assays for the detection of patients sensitized to halothane. *Anesthesia and Analgesia* 1990; 70: 154-159.
- Goldberger R, Anfinsen C. The reversible masking amino groups in ribonuclease and its possible usefulness in the synthesis of the protein. *Biochemistry* 1962; 1: 401-405.
- Soltis JJ, Gandolfi AJ. Detection of fluorinated anesthetic metabolites by sodium fusion. *Anesthesia and Analgesia* 1980; 59: 61-64.
- Lind RC, Gandolfi AJ, Sipes IG, Brown BR, Waters SJ. Oxygen concentrations required for reductive defluorination of halothane by rat hepatic microsomes. *Anesthesia and Analgesia* 1986; 65: 835-839.
- Callis AH, Brooks SD, Roth TP, Gandolfi AJ, Brown BR. Characterization of a halothane-induced humoral immune response in rabbits. *Clinical Experimental Immunology* 1987; 67: 343-351.
- Kenna JG, Neuberger J, Williams R. An enzyme-linked immunosorbent assay for detection of antibodies against halothane-altered hepatocyte antigens. *Journal of Immunology Methods* 1984; 75: 3-14.
- Kenna JG, Major GN, Williams RS. Methods for reducing non-specific antibody binding in enzyme-linked immunosorbent assays. *Journal of Immunology Methods* 1985; 85: 409-419.
- Satoh H, Gillette JR, Takemura T, Ferrans VJ, Jelenich SE, Kenna JG, Neuberger J, Pohl LR. Investigation of the immunological basis of halothane-induced hepatotoxicity. In: Kocsis JJ, Jollow DJ, Witmer CM, Nelson JO, Snyder R, eds. *Biological Reactive Intermediates*, Vol. III. New York: Plenum Press, 1985; 657-673.
- Hubbard AK, Roth TP, Gandolfi AJ, Brown BR, Webster NR, Nunn JF. Halothane hepatitis patients generate an antibody response toward a covalently bound metabolite of halothane. *Anesthesiology* 1988; 68: 791-796.
- Bird GLA, Williams R. Detection of antibodies to a halothane metabolite hapten in sera from patients with halothane-associated hepatitis. *Journal of Hepatology* 1989; 9: 366-373.
- Kenna JG, Neuberger J, Williams R. Specific antibodies to halothane-induced liver antigens in halothane-associated hepatitis. *British Journal of Anaesthesia* 1987; 59: 1286-1290.

PROTEIN METABOLISM AFTER ABDOMINAL SURGERY: EFFECT OF 24-H EXTRADURAL BLOCK WITH LOCAL ANAESTHETIC

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SUMMARY

We have studied the effect of intraoperative and postoperative (24 h) extradural block with local anaesthetic on whole body protein turnover (stable isotope methodology) and urinary excretion of urea nitrogen, adrenaline, noradrenaline and cortisol in a group of well nourished elderly patients undergoing colorectal surgery who received a constant nutritional intake before (7 days) and after (4 days) surgery. One group (control, n = 8) received routine anaesthetic and surgical care. Patients in the test group (extradural, n = 9) received extradural bupivacaine, and sensory block (T4-S5) was maintained during and after surgery for a period of 24 h. Whole body protein breakdown and aminoacid oxidation increased significantly after surgery in both groups ($P < 0.05$), but the increase in protein breakdown in the extradural group was significantly less than that in the control group. Urinary excretion of urea nitrogen, adrenaline and noradrenaline increased in the control group after surgery, whilst the increase in the extradural group was very small. In contrast, urinary excretion of cortisol increased significantly in both groups after surgery. We conclude that extradural block maintained for 24 h after surgery significantly minimized postoperative protein breakdown without compromising whole body protein synthesis.

KEY WORDS

Metabolism: protein. Anaesthetic techniques: extradural.

The metabolic response to surgery is associated with a negative nitrogen balance that results from

a decrease in whole body protein synthesis, an increase in whole body protein breakdown or a combination of both.

Interpretation of injury-induced perturbations of protein metabolism must be considered in the light of preoperative nutritional status, postoperative nutritional intake and the intensity of trauma. A recent study has focused on the protein kinetic response to surgery under rigidly controlled nutritional conditions [1].

Administration of local anaesthetics via the extradural route prevents a major part of the classical endocrine-metabolic response to surgical procedures including lower abdominal surgery and operations on the lower extremities [2]. Brandt and colleagues [3] reported significantly less negative cumulative nitrogen balance after surgery in patients who received extradural anaesthesia for abdominal hysterectomy compared with general anaesthesia. Vendrinne and colleagues [4] observed a significant decrease in urinary excretion of 3-methylhistidine, an indicator of protein catabolism, in patients who underwent colonic surgery and received continuous extradural bupivacaine for 48 h after surgery.

The present study was designed to evaluate changes in whole body protein turnover and catabolic hormones during the postoperative

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period in patients who received extradural local anaesthetics during surgery and for a period of 24 h after surgery. Intake of protein and calories was maintained constant throughout the preoperative and postoperative periods.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of Northwick Park Hospital and informed consent was obtained from 17 patients undergoing anterior resection; in all subjects the cancer of the sigmoid-rectum was a single localized lesion with no metastases. None of the patients had cardiac, hepatic, renal or metabolic disorders, or suffered from protein-calorie malnutrition.

Mean (SD) preoperative plasma albumin concentration in the two groups was 37 (2) g litre⁻¹ and 38 (2) g litre⁻¹. Patients were admitted to the metabolic ward and an oral daily diet based on nitrogen 0.1 g kg⁻¹ and 84 J kg⁻¹ (60 % fat, 35 % carbohydrate and 5 % protein contribution) was started 6 days before surgery, under dietetic supervision. The same amount of energy and nitrogen was administered i.v. and commenced 6–8 h from the end of surgery and continued for 4 days after surgery. The parenteral nutrition (KabiVitrum, Stockholm, Sweden) was administered via a peripheral cannula at a constant rate via an infusion pump (IMED 928, IMED, Milton). Skinfold thicknesses (biceps, triceps, subscapular, iliac crest) and mid-arm circumference were measured on the day before surgery and the percentage of body fat calculated [5].

Patients were allocated randomly to two groups (control or extradural) of eight and nine patients, respectively, to receive either general anaesthesia alone or extradural block supplemented by a general anaesthesia. Premedication comprised papaveretum 10–20 mg and hyoscine 0.2–0.4 mg i.m. 60 min before surgery. General anaesthesia was induced with thiopentone and neuromuscular block obtained with pancuronium. The lungs were ventilated to normocapnia ($\dot{V}'_{CO_2}$, 4.5–5.5 %) with 70 % nitrous oxide and enflurane in oxygen.

In the extradural group, an extradural catheter was inserted between T9 and T11 and 0.75 % bupivacaine 15–20 ml was injected to produce segmental sensory block from T4 to S5. Additional local anaesthetic (5–10 ml) was injected into the extradural space 1–2 h later. At the end of surgery, extradural 0.25 % bupivacaine was in-

fused continuously at a rate of 10–15 ml h⁻¹ and maintained for 24 h. During this period sensory analgesia from T4 to S5 was assessed 2-hourly and when necessary a further dose of bupivacaine administered. In both groups, i.m. papaveretum was given when required for postoperative analgesia. During surgery all patients received an i.v. infusion of Hartmann's solution 6 ml kg⁻¹ h⁻¹. Whole blood was administered when blood loss exceeded 20 % of the patient's blood volume.

All operations started between 08:30 and 10:30 and were performed by the same surgical team.

Protein turnover studies

Oral and i.v. nutrition were withheld from midnight before the morning of the studies, which were conducted between 08:00 and 12:00. The isotope infusions were carried out in all patients on the day before surgery and on days 2 and 4 after surgery. A superficial vein in the dorsum of one hand was cannulated and the cannula kept patent with heparinized saline. A second superficial vein in the contralateral arm was cannulated to provide access for infusion of L-[1-¹³C]leucine. Blood and expired air samples were collected before the infusion to determine baseline carbon-13 enrichment. Primed doses of [¹³C]NaHCO₃ 0.08 mg kg⁻¹ and L-[1-¹³C]leucine 0.5 mg kg⁻¹ were administered, followed immediately by a continuous infusion of L-[1-¹³C]leucine 0.5 mg kg⁻¹ which was maintained for 4 h. All isotope solutions were prepared by the hospital pharmacy and shown to be sterile and pyrogen free.

Venous blood and expired air samples were collected every 15 min during the final 2 h of the infusion period; it has been demonstrated that during this time an isotope steady state is achieved. Each blood sample was transferred to a pre-cooled heparinized tube, centrifuged at 4 °C and the plasma stored at -70 °C until α -ketoisocaproate (α -KIC) enrichment could be measured. Expired air samples were collected in a 2-litre latex bag and transferred immediately by syringe to duplicate 20-ml Vacutainers (Beckton, Dickinson) to await [¹³C]carbon dioxide enrichment analysis. Oxygen consumption and carbon dioxide production were measured by indirect calorimetry using a previously calibrated metabolic monitor (Datex, Helsinki, Finland) during the 2-h isotope plateau on each day of the study.

Whole body leucine kinetics were calculated by conventional isotope dilution methodology using

a two-pool stochastic model during steady state conditions [6]. Plasma enrichment of α -KIC was used as the basis for calculating both the flux and oxidation rate of leucine. Plasma α -KIC enrichment and concentration were measured by electron impact selected-ion monitoring gas chromatography-mass spectrometry, using keto-valeric acid as internal standard [7]. Expired breath [^{13}C]carbon dioxide enrichment was measured on the day of the study by isotope ratio mass spectrometry and used to calculate leucine oxidation. A factor of 0.81 was applied to account for the fraction of [^{13}C]carbon dioxide released by [^{13}C]leucine oxidation but retained within slow turnover rate of pools of the body [8].

Urinary urea nitrogen, creatinine, adrenaline, noradrenaline and cortisol concentrations

Urine was collected for a 24-h period on two consecutive days before surgery and four consecutive days after surgery. Aliquots were analysed for concentrations of urea nitrogen, creatinine, adrenaline, noradrenaline and cortisol. Urea nitrogen and creatinine were determined by the SMAC automated procedure. Urinary catecholamines were measured by reverse-phase ion-paired high pressure liquid chromatography with electrochemical detection [9] and urinary cortisol was measured by a fluorimetric method [10]. All measurements of metabolites and hormones were performed in duplicate.

C-reactive protein

Blood samples were taken before, and 2 and 4 days after surgery to monitor acute phase response by measurement of C-reactive protein using an immunoturbidimetric assay [11].

Statistical analysis

Results are expressed as mean and range or SD or SEM. Analysis of variance was performed for flux, oxidation and synthesis. Two factors were included in the analysis: treatment and time. Treatment comparisons were made between groups, while time comparisons were made within groups. For all these analyses, the normality of residuals and equality of residual variances were tested using Shapiro Wilk's test and Schweder's test, respectively. These tests revealed one person with extreme results which were excluded from the analysis, leaving two groups of eight. A summary measure was determined for urinary nitrogen, creatinine, adrenaline and noradrenaline

concentrations, and this was the difference between 1 day postoperative and preoperative values. The variability in this measurement differed between the control and extradural groups and therefore a Mann-Whitney test was used to compare the groups.

RESULTS

Patient characteristics were comparable in the two groups (tables I, II). The total amount of papaveretum administered during the first 24 h after surgery in the control group was 95 (SD 22) mg, compared with 32 (18) mg in the extradural group ($P < 0.05$).

TABLE I. Patient data (mean (range))

	Control (n = 8)	Extradural (n = 8)
Sex (M:F)	2:6	3:5
Age (yr)	68 (58-75)	70 (59-78)
Weight (kg)	55 (40-72)	57 (52-67)
BMI (kg m^{-2})	22 (17-29)	21 (17-27)
Fat (%)	29 (26-32)	28 (25-33)

TABLE II. Clinical data (mean (range))

	Control (n = 8)	Extradural (n = 8)
Preoperative starvation (h)	14 (11-16)	13 (12-16)
Duration of surgery (min)	178 (170-200)	185 (165-200)
Blood loss (ml)	937 (620-1150)	878 (550-1040)

TABLE III. Mean (SEM) values of whole body protein flux/breakdown, oxidation and synthesis before and after surgery

Treatment	Protein ($\mu\text{mol kg}^{-1} \text{h}^{-1}$)			
	Before surgery	2 days after surgery	4 days after surgery	SEM
Flux				
Control (n = 8)	117.3	162.0	158.8	5.41
Extradural (n = 8)	139.3	154.2	156.4	5.41
Oxidation				
Control (n = 8)	15.8	30.0	32.6	1.88
Extradural (n = 8)	21.3	28.2	31.0	1.88
Synthesis				
Control (n = 8)	101.6	132.0	126.2	4.65
Extradural (n = 8)	118.1	126.1	125.4	4.65

TABLE IV. Differences between average postoperative (over 2 and 4 days) and preoperative values of protein turnover

Treatment	Difference	95 % Confidence interval	P
Flux			
Control (n = 8)	14.3	9.8–18.8	< 0.001
Extradural (n = 8)	5.3	0.8–9.8	< 0.023
Oxidation			
Control (n = 8)	5.2	3.6–6.8	< 0.001
Extradural (n = 8)	2.8	1.2–4.4	0.001
Synthesis			
Control (n = 8)	9.2	5.3–13.1	< 0.001
Extradural (n = 8)	2.6	–1.3–6.5	0.182

Preoperative protein data were comparable in the two groups. Analysis of variance showed that there was no significant difference between the 2nd and the 4th days postoperative values for flux ($P = 0.9$), oxidation ($P = 0.15$) and synthesis ($P = 0.5$). The difference between the average postoperative values over 2 and 4 days, and the preoperative values were found to be significantly different between treatments for flux ($P = 0.07$), oxidation ($P = 0.035$) and synthesis ($P = 0.02$) (table III). There was a significant increase between preoperative and average postoperative

values for flux and oxidation in both groups, and for synthesis in the control group (table IV). In all variables the increase in the control group was greater than in the extradural group.

Urinary urea nitrogen concentration increased in the control group after surgery by more than 50 % during the first day after operation and remained increased thereafter. In contrast, there was a small increase in the extradural group. These changes were significantly different between the two groups ($P < 0.001$). Urinary creatinine increased after surgery in both groups, and there was a small, but not significant difference between the two groups ($P = 0.052$) (table V).

Both urinary adrenaline and noradrenaline concentrations increased after surgery in the control group, but there was little change in the extradural group. The change after surgery was significantly different between the groups ($P < 0.001$) for both variables. Urinary cortisol excretion increased significantly ($P < 0.001$) after surgery in both groups, but there was no significant difference between groups (table V).

Preoperative C-reactive protein was 3.1 (3.7) ng litre⁻¹ in the control group and 1.8 (1.1) ng litre⁻¹ in the extradural group. These values increased significantly ($P < 0.001$) 24 h after surgery to 77.3 (42.1) ng litre⁻¹ in the control

TABLE V. Urinary excretion (mean (SD)) of urea nitrogen, creatinine, adrenaline, noradrenaline and cortisol in the two groups

	Before surgery	After surgery			
	Day -1	Day +1	Day +2	Day +3	Day +4
Urea nitrogen (mmol day ⁻¹)					
Control	84 (9)	124 (12)	126 (19)	119 (16)	113 (16)
Extradural	81 (14)	84 (17)	84 (18)	90 (18)	89 (17)
Creatinine (mmol day ⁻¹)					
Control	6 (3)	13 (5)	14 (6)	12 (5)	12 (5)
Extradural	5 (3)	10 (4)	10 (5)	10 (5)	8 (4)
Adrenaline (µmol day ⁻¹)					
Control	0.05 (0.03)	0.31 (0.13)	0.02 (0.08)	0.12 (0.04)	0.10 (0.04)
Extradural	0.04 (0.03)	0.09 (0.03)	0.06 (0.03)	0.04 (0.03)	0.04 (0.02)
Noradrenaline (µmol day ⁻¹)					
Control	0.15 (0.04)	0.43 (0.16)	0.41 (0.15)	0.36 (0.14)	0.36 (0.13)
Extradural	0.19 (0.08)	0.23 (0.08)	0.21 (0.09)	0.20 (0.08)	0.18 (0.07)
Cortisol (nmol day ⁻¹)					
Control	379 (162)	3391 (760)	—	2235 (643)	—
Extradural	412 (125)	2970 (410)	—	2127 (782)	—

group and 96.5 (28.2) ng litre⁻¹ in the extradural group.

DISCUSSION

We have shown that extradural anaesthesia with local anaesthetic established before surgery and maintained for 24 h after surgery minimized postoperative loss of protein over a period of 4 days.

Negative nitrogen balance develops after surgery and it has not been possible to restore equilibrium by nutritional means alone in the immediate postoperative period in the non-depleted patient [12]. Because of the problems with use of nitrogen balance as a criterion for assessing protein metabolism, and the influence of perioperative nutritional status on protein turnover, we have used stable isotopes to provide a more dynamic and direct determination of whole body protein metabolism by measuring protein flux or breakdown, leucine oxidation and synthesis [13]. The significantly smaller increase in whole body protein breakdown and aminoacid oxidation after surgery, associated with the small, but not significant, change in synthesis observed in the extradural group, strongly suggests that extradural anaesthesia was effective in attenuating protein loss, without affecting whole body protein synthesis.

Although our patients had cancer, none suffered from protein-calorie malnutrition as shown by the normal range of anthropometric indices and plasma concentration of albumin before surgery. The possible effect of a malignant tumour on protein metabolism of the host has been considered in previous studies [14, 15], and although the preoperative values of whole body protein turnover in both groups were increased, they were not significantly different from protein turnover in non-cancer patients reported earlier [1].

Previous reports have demonstrated the beneficial effect of extradural anaesthesia on nitrogen balance and protein metabolism; however, deficiencies in controlling different variables led to contrasting results. Brandt and colleagues [3] showed significantly less negative postoperative cumulative nitrogen balance in patients who received extradural anaesthesia for abdominal hysterectomy compared with general anaesthesia. Later, in a study similar to the present investigation, where nutritional intake was controlled, Vendrinne and colleagues [4], reported signif-

icantly less urinary excretion of 3-methylhistidine in an extradural group. In contrast, Hjortso and colleagues [16] reported that extradural analgesia failed to prevent nitrogen loss after abdominal surgery; however, they studied patients undergoing either lower or upper abdominal surgery in whom preoperative and postoperative nitrogen and energy intakes were not well controlled.

The extent of the extradural block needed to decrease the neuronal afferent input (T4-S5) and its duration (more than 24 h) appear to be essential variables if a prolonged effect on intermediary metabolism is required. This has been shown in early studies on the influence of spinal anaesthesia on the metabolic response to surgery [2] and more recently by Carli and Emery [17] who were unable to attenuate the postoperative loss of body protein in patients who had an extradural block from T8 to S4 limited only to the period of surgery.

The high concentration of urinary cortisol observed in the extradural group after surgery suggests that the regimen used in this study was not sufficient to provide afferent block capable of preventing the increased concentration of circulating cortisol. However, there is no agreement on whether or not this hormone plays a significant role in modulating protein catabolism. While Christensen and colleagues [18] reported that glutamine efflux from muscle remained at preoperative values when extradural anaesthesia was used, Hulton and colleagues [19] were unable to demonstrate in dogs any effect of extradural block on muscle proteolysis, despite a suppressed increase in circulating concentration of cortisol. It remains to be established if other hormones or humoral factors such as cytokines are directly responsible for modulating protein metabolism.

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REFERENCES

1. Carli F, Webster J, Ramachandra V, Pearson M, Read M, Ford GC, McArthur S, Preedy VR, Halliday D. Aspects of protein metabolism after elective surgery in patients receiving constant nutritional support. *Clinical Science* 1990; 78: 621-628.

2. Kehlet H. The modifying effect of general and regional anaesthesia on the endocrine-metabolic response to surgery. *Regional Anaesthesia* 1982; 7: 38-48.
3. Brandt MR, Fernandes A, Mordhorst R, Kehlet H. Epidural analgesia improves postoperative nitrogen balance. *British Medical Journal* 1978; 1: 1106-1108.
4. Vedrinne C, Vedrinne JM, Guiraud M, Patricet MC, Bouletreau P. Nitrogen-sparing effect of epidural administration of local anesthetics in colon surgery. *Anesthesia and Analgesia* 1989; 69: 354-359.
5. Durnin JVG, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged 16 to 72 years. *British Journal of Nutrition* 1974; 32: 77-97.
6. Schwenk WF, Beaufre B, Haymond MW. Use of reciprocal pool specific activities to model leucine metabolism in human. *American Journal of Physiology* 1985; 249: E646-650.
7. Ford GC, Cheng KN, Halliday D. The analysis of [1-¹³C]leucine and ¹³C- α -KIC in plasma by capillary gas chromatography/mass spectrometry in protein turnover studies. *Biomedical Mass Spectrometry* 1985; 12: 432-436.
8. Matthews DE, Motil KJ, Rohrbach DK, Burke JF, Young VR, Bier DM. Measurement of leucine metabolism in man from a primed, continuous infusion of L-[1-¹³C]leucine. *American Journal of Physiology* 1980; 238: E473-479.
9. Molnar J, Horwath C. Reverse phase chromatography of polar biological substances: separation of catechol compounds by high performance liquid chromatography. *Clinical Chemistry* 1976; 22: 1496-1502.
10. Mattingly D. A simple fluorimetric method for the estimation of free 10-hydroxycorticosteroids in human plasma. *Journal of Clinical Pathology* 1962; 15: 374-379.
11. Price CP, Trull AK, Berry D, Gorman EG. Development and validation of a particle-enhanced turbidimetric immunoassay for C-reactive protein. *Journal of Immunological Methods* 1987; 99: 205-224.
12. Fellows IW, Woolfson AMJ. Effects of therapeutic intervention on the metabolic responses to injury. *British Medical Bulletin* 1985; 42: 287-294.
13. Halliday D, Rennie MJ. The use of stable isotope for diagnosis and clinical research. *Clinical Science* 1987; 63: 485-496.
14. Carmichael MJ, Clague MB, Keir MJ, Johnston IDA. Whole body protein turnover, synthesis and breakdown in patients with colorectal carcinoma. *British Journal of Surgery* 1980; 67: 736-739.
15. Glass RF, Fern EB, Garlick PJ. Whole body protein turnover before and after resection of colorectal tumours. *Clinical Science* 1983; 64: 101-108.
16. Hjortso NC, Christensen NJ, Andersen T, Kehlet H. Effects of the extradural administration of local anaesthetic agents and morphine on the urinary excretion of cortisol, catecholamines and nitrogen following abdominal surgery. *British Journal of Anaesthesia* 1985; 57: 400-406.
17. Carli G, Emery PW. Intraoperative epidural blockade with local anaesthetics and postoperative protein breakdown associated with hip surgery in elderly patients. *Acta Anaesthesiologica Scandinavica* 1990; 34: 263-267.
18. Christensen T, Waaben J, Lindeburg T, Vesterberg K, Vinnars E, Kehlet H. Effect of epidural analgesia in muscle amino acid pattern after surgery. *Acta Chirurgica Scandinavica* 1986; 152: 407-411.
19. Hulton N, Johnson DJ, Smith RJ, Wilmore DW. Hormonal blockade modifies post-traumatic protein catabolism. *Journal of Surgical Research* 1985; 39: 310-315.

EFFECTS OF LOW CONCENTRATIONS OF CYCLOPROPANE AND HALOTHANE ON PEAK VELOCITY OF SACCADIC EYE MOVEMENTS

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SUMMARY

We have investigated the effect of 4.7 and 8.8% MAC of cyclopropane, and 5.3 and 9.3% MAC of halothane on the peak velocity of saccadic eye movements (PSV) in six healthy volunteers. Both concentrations of cyclopropane and halothane significantly depressed PSV ($P < 0.01$) compared with air, in a dose-related fashion. Halothane depressed PSV significantly more than cyclopropane ($P < 0.05$). PSV returned to baseline within 5 min after discontinuation of the agents. There was no significant difference between cyclopropane, halothane and air in subjective assessment of sedation.

KEY WORDS

Anaesthetics volatile: cyclopropane, halothane. Brain: monitoring, saccadic eye movements.

Saccadic eye movements are the fastest movement of which the oculomotor system is capable. The peak velocity of saccadic eye movement (PSV) is thought to be an indicator of the functional state of a well defined group of neurones in the brainstem reticular formation [1] and, besides being a sensitive indicator of CNS depression, has the advantage of being beyond voluntary control [2]. In a previous study [3], 5 and 10% MAC of isoflurane were found to depress PSV, whereas the effects of equi-MAC concentrations of nitrous oxide were indistinguishable from those of air. One hypothesis to explain the difference between the agents is the sympathetic stimulating effect of nitrous oxide [4, 5]. Cyclopropane has a similar stimulating effect [6, 7]. We have therefore investigated this hypothesis by comparing the

effect on PSV of 5% and 10% MAC concentrations of cyclopropane with halothane, an agent generally regarded as similar to isoflurane [8].

The aims of this study were to determine if 5% and 10% MAC concentrations of cyclopropane and halothane affect PSV, if these effects were the same for both agents and if there was a dose-effect relationship.

SUBJECTS AND METHODS

We studied six drug-free healthy volunteers, aged 21-33 yr. Informed consent was obtained from each subject and the study was approved by the local Ethics Committee. The study consisted of three treatment sessions given at intervals of 1 week or greater. Each session consisted of assessment while breathing air or 5% and 10% MAC concentrations of one of the test agents. The agents were administered in a random order determined by opening the next envelope in a pregenerated set of six sets of the three sequences. Each volunteer was allowed to practise the saccadic eye movement task before the formal sessions until there was no learning effect.

Breathing system

Concentrations of 0.5-1% cyclopropane in air were delivered by a Boyle anaesthetic machine with a total fresh gas flow of 12 litre min⁻¹. Concentrations of 0.05-0.14% halothane were delivered using a calibrated Fluotec 3 vaporizer

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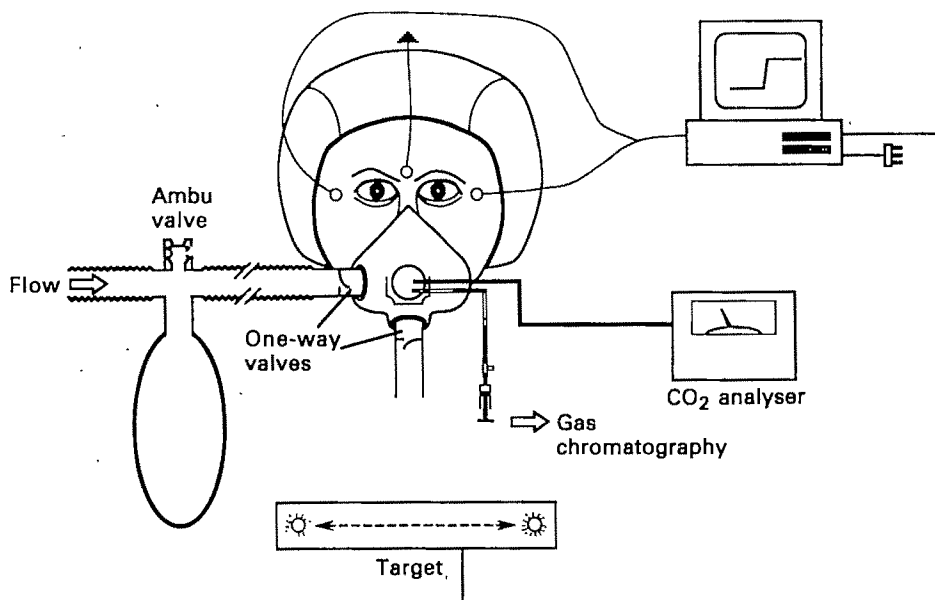


FIG. 1. Diagram of breathing system and experimental arrangements.

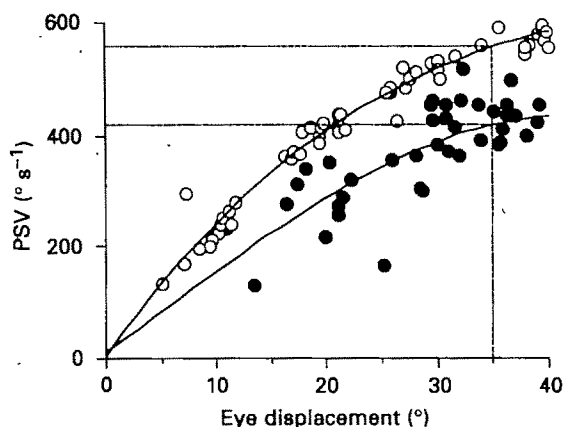


FIG. 2. Relationship between eye displacement (degrees) and PSV, with fitted quadratic curves, for air (○) and halothane (●). The interpolated value at 35° was taken as the PSV measure.

and diluting the output concentrations with air via a second calibrated flowmeter with a total fresh gas flow of 12–22 litre min⁻¹. The inspiratory concentrations were adjusted to maintain as near as 5% and 10% MAC of end-tidal concentrations as possible (0.46 and 0.92% cyclopropane; 0.038 and 0.076% halothane [9]), based on the NARKUP computer program [10] adjusted for the subject's age, sex, height and body weight. In the case of halothane, overpressure was applied

for 10 min by giving approximately 2–2.5 times the required concentration and this was followed by the maintenance concentration for 20 min.

The breathing system is shown in figure 1. An Ambu valve was inserted into the inspiratory limb of the breathing system to avoid the expired gas being diluted by excess fresh gas. Each volunteer wore a Royal Air Force pilot's face mask with non-rebreathing valves. Two fine bore tubes were attached to the mask and alveolar gas samples were taken through one tube at 10-min intervals just before each PSV measurement. Expired carbon dioxide was monitored continuously with a Normcap 200 infra-red analyser through the other sample tube to identify the alveolar plateau. Cyclopropane and halothane concentrations were measured by gas-liquid chromatography calibrated by standard gas mixtures. Halothane standards in the range 0.02–0.2 vol% were prepared in gas-tight glass jars of known volume using a weighed aliquot of liquid halothane and treating the vapour as if it were an ideal gas. In the case of cyclopropane, a calculated volume of pure gas was taken from a Boyle anaesthetic machine by a syringe to obtain standards between 0.5 and 1 vol%.

Saccadic eye movement measurements

Complete details of the eye movement recording system have been reported in two previous

papers [3, 11]. In brief, saccades were generated by requiring the subject to follow the horizontal movements of an illuminated target. An IBM compatible (Opus PC II) microcomputer controlled the target movements (fig. 1). The target was moved every 1.5 s instantaneously in a pre-determined pattern designed to generate 24 analysable saccades at symmetrical eye displacements of 10°, 20°, 30° and 40°. Three such sequences were taken with 20-s intervals at each measurement point.

Eye position was monitored from the electro-oculogram (EOG), which was measured from stick-on silver-silver chloride electrodes placed lateral to both outer canthi, and a reference electrode on the forehead (fig. 1). Electrode resistances were always less than 4 k Ω . The EOG was d.c. amplified, low-pass filtered (-3 dB at 50 Hz) before being digitized to 12-bit resolution at a sampling frequency of 250 Hz and stored on disk.

Saccades were analysed in two stages according to the method of Marshall and Richens [12]. The digitized data from each target displacement were first processed to locate saccades. Each saccade was analysed to extract the size of the saccade in degrees and the PSV in degrees per second. Few saccades are completely accurate and so the size of the saccade may be greater (overshoot) or less (undershoot) than the target displacement. Because peak velocity is determined by the size of the saccade and not the size of the target displacement, it is necessary to model the velocity-saccade size relationship and calculate the velocity achieved for a defined saccade size. Saccades show a unique feature: the greater the angular eye movement up to about 30–35°, the greater the peak velocity. Therefore the relationship between the degree of eye displacement and PSV was modelled for each measurement occasion, by fitting a quadratic curve to the displacement-velocity relationship. The interpolated value at 35° was taken as the measure in this study (fig. 2). (There is always greater variability in the displacement-velocity points with volatile agents than with air, and this variability increases with increasing concentrations. At concentrations greater than those used in this study, the combination of increased variability and "missed" values renders the measurement of PSV unreliable.)

Each session started with a 15-min baseline period with the subject breathing air, followed by

30 min each of approximately 5% and 10% MAC and 10 min for recovery breathing air. PSV was measured at 5-min intervals during the baseline period, at 10-min intervals during the inhalation of 5% and 10% MAC and once during the recovery period. An additional measurement was made after a 15-min break without the face mask. All the PSV measurements were normalized by dividing the values by the mean of the baseline measurements on that treatment day. These normalized PSV values at 15 and 25 min at each anaesthetic concentration were averaged and the means were compared with control air values by Student's two-tailed *t* test. As the study was designed to answer specific questions, a multiple comparisons correction was not applied [13].

Subjective assessments

Each subject was asked to assess their degree of sedation by marking a 10-cm linear analogue scale each time just before the PSV measurements. The extremes were denoted as "wide awake" and "just before falling asleep". All visual analogue scores (VAS) were normalized by subtracting the mean of the baseline measurements on that day. Wilcoxon's rank sum test was applied to normalized VAS. Subjects were also asked about the presence or absence of odour, headache and nausea at the end of each treatment, and Fisher's test of exact probability was applied to the responses.

RESULTS

The normalized PSV values at 35°, the visual analogue scores and the end-tidal concentrations of cyclopropane and halothane are plotted in figure 3. Mean end-tidal concentrations of cyclopropane were 4.7 (SEM 0.3)% and 8.8 (0.8)% of MAC and those of halothane were 5.3 (0.5)% and 9.3 (0.5)% of MAC, respectively, at 15 and 25 min of each session. End-tidal concentrations of carbon dioxide were always in the range 4–5% with each concentration of each agent. Both cyclopropane and halothane caused a highly significant ($P < 0.01$) dose-related depression of PSV. Depression of PSV by halothane was significantly greater than that caused by cyclopropane ($P < 0.05$) (fig. 3). To correct for the actual concentrations not being exactly 5 or 10% of MAC, the grand mean of all concentrations of both agents was calculated and found to be 7.0 (0.5)% of MAC. The PSV values

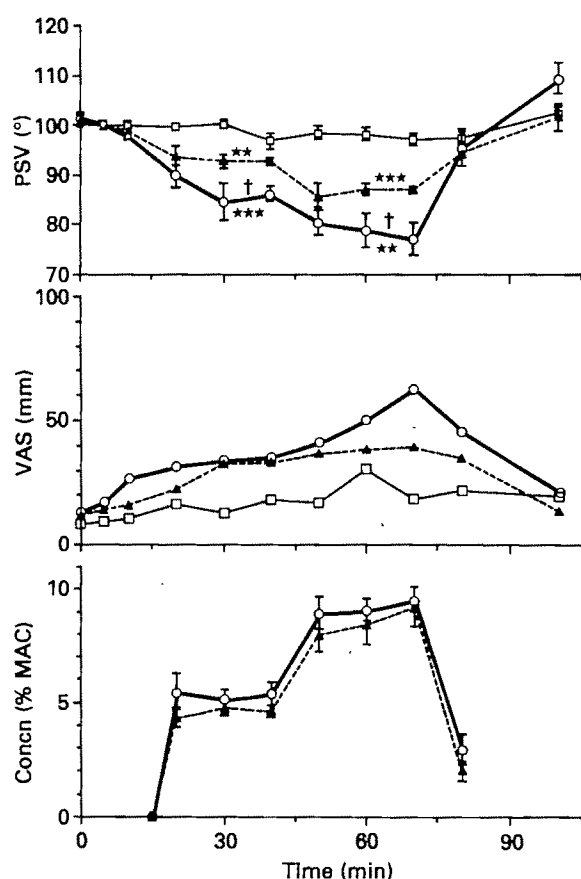


FIG. 3. Mean (SEM) effect of 5% and 10% MAC concentrations of cyclopropane ($\blacktriangle$), halothane ($\circ$) and air ($\square$) on normalized PSV and VAS, and end-tidal concentrations (Concn) (as a percentage of MAC) of cyclopropane ($\blacktriangle$) and halothane ($\circ$) in six volunteers. ** $P < 0.01$; *** $P < 0.001$ compared with air; † $P < 0.05$ cyclopropane compared with halothane.

for each agent were interpolated for this concentration. Cyclopropane caused an 88.9 (1.4)% reduction in normalized PSV and halothane a 82.0 (2.2)% reduction (fig. 4) ($P < 0.05$). PSV had returned to baseline values within 5 min of discontinuation of the anaesthetic agents. End-tidal concentrations at this time were 2.1 (0.4)% of MAC for cyclopropane and 3.0 (0.7)% of MAC for halothane.

There was no significant differences in VAS between air and either cyclopropane or halothane (fig. 3). Subjective assessment of the appreciation of odour, the feeling of nausea and headache under each treatment are shown in table I. The only significant difference between the agents was detection of odour between halothane and air.

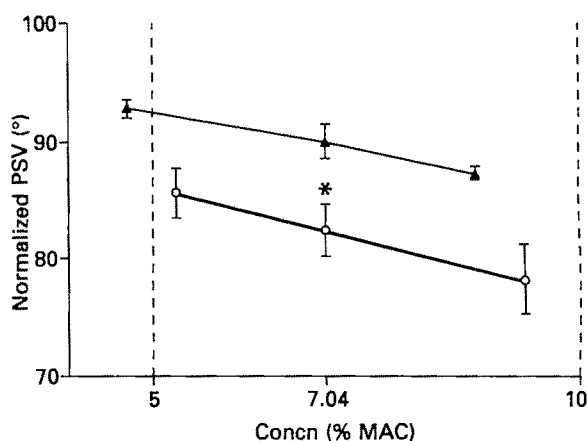


FIG. 4. Mean (SEM) normalized PSV of cyclopropane ($\blacktriangle$) and halothane ($\circ$) interpolated at the grand mean concentration of 7.04% MAC in six volunteers. * $P < 0.05$ cyclopropane compared with halothane.

TABLE I. Subjective assessments of odour, nausea and headache. A = Air, C = cyclopropane and H = halothane. ** $P < 0.01$ compared with air

	A	C	H
Odour			
Present	0	3	6**
Absent	6	3	0
Nausea			
Present	0	0	2
Absent	6	6	4
Headache			
Present	0	1	0
Absent	6	5	6

DISCUSSION

Our results show that both cyclopropane and halothane caused dose-dependent depression of PSV and that depression with halothane was significantly greater than with cyclopropane at equivalent sub-anaesthetic concentrations.

The brain tension of cyclopropane quickly equilibrates with a constant inspired tension because of the low solubility of cyclopropane in blood and brain tissue. This is not true of halothane. The NARKUP computer program [10] was run with the same profile of inspired concentrations as in the experiment, and the values of brain and alveolar tension were computed at 15 and 25 min and averaged. The computed alveolar concentrations were in good agreement with the measured values (table II).

TABLE II. Means of results at 15 and 25 min in each session

	Alveolar concentrations		Computed brain:alveolar tension	Estimated brain tension (% MAC)
	Measured (vol %)	Computed (vol %)		
Cyclopropane				
5 % MAC	0.434	0.430	0.88	4.145
10 % MAC	0.812	0.880	0.96	8.503
Halothane				
5 % MAC	0.040	0.035	0.90	4.773
10 % MAC	0.071	0.070	0.89	8.275

Therefore the brain tension in MAC units was estimated for each subject from the individual measured alveolar concentrations and the computed brain:alveolar tension ratio (table II). Accordingly, the averages of normalized PSV at 15 and 25 min could be compared for each session.

The end-tidal concentrations of both agents were smaller than the target concentrations of 5 % and 10 % MAC, mainly because we were not able to monitor end-tidal concentrations continuously.

VAS for sedation failed to differentiate both cyclopropane and halothane from air. Two of six subjects showed improvement in VAS for sedation while alveolar concentrations were increasing, although PSV was progressively depressed. This suggests that subjective assessments are an unsatisfactory indicator of mild CNS depression, a conclusion reached by Gao, Marshall and Vickers for isoflurane [3], and by Gao, Mapleson and Vickers for propofol [11].

Although direct comparisons are not possible, this study, using identical methodology and many of the same volunteers, found that halothane had effects identical to those of isoflurane at almost equi-sub-MAC concentrations [3]. However, cyclopropane was not similar to nitrous oxide, but produced an intermediate effect. The similarity between halothane and isoflurane is not unexpected [8]. Although both cyclopropane and nitrous oxide have a sympathetic stimulating effect [4-7] the lesser depression by cyclopropane compared with halothane and isoflurane supports the conclusion that a sympathetic stimulating effect may be relevant to this difference from nitrous oxide. The results do not, however, explain why equi-sub-MAC concentrations of the different inhalation agents have such different effects.

The result of this study, together with those of Gao, Marshall and Vickers [3] indicate that equi-

sub-MAC concentrations of halothane and isoflurane have comparable and marked effects, nitrous oxide has no detectable effect and cyclopropane has an intermediate effect on PSV. This is further confirmation that it is too simplistic to think that equi-MAC concentrations of inhalation agents have equivalent actions throughout the CNS.

ACKNOWLEDGEMENT

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REFERENCES

1. Keller EL. Participation of medial pontine reticular formation in eye movement generation in the monkey. *Journal of Neurophysiology* 1974; 37: 316-332.
2. Griffiths AN, Marshall RW, Richens A. Saccadic eye movement analysis as a measure of drug effects on human psychomotor performance. *British Journal of Clinical Pharmacology* 1984; 18: 73S-82S.
3. Gao F, Marshall RW, Vickers MD. Effect of low concentrations of nitrous oxide and isoflurane on peak velocity of saccadic eye movements. *British Journal of Anaesthesia* 1991; 66: 179-184.
4. Millar RA, Warden JC, Cooperman LH, Price HL. Central sympathetic discharge and mean arterial pressure during halothane anaesthesia. *British Journal of Anaesthesia* 1969; 41: 918-928.
5. Fukunaga AF, Epstein RM. Sympathetic excitation during nitrous oxide-halothane anesthesia in the cat. *Anesthesiology* 1973; 39: 23-36.
6. Price HL, Warden JC, Cooperman LH, Millar RA. Central sympathetic excitation caused by cyclopropane. *Anesthesiology* 1969; 30: 426-438.
7. Fukunaga AF, Epstein RM. Effects of cyclopropane on the sympathetic nervous system and on neural regulation of circulation in the cat. *Anesthesiology* 1974; 40: 323-339.
8. White DC. Appraisal of inhalational anaesthetic agents. In: Kaufman L, ed. *Anaesthesia Review* 3. London: Churchill Livingstone, 1985; 110-121.
9. Saidman LJ, Eger EI II, Munson ES, Babad AA, Muallem M. Minimum alveolar concentrations of methoxyflurane, halothane, ether and cyclopropane in man: Correlation with theories of anesthesia. *Anesthesiology* 1967; 28: 994-1002.

10. Lockwood GG, White DC. NARKUP: A program demonstrating the effect on anaesthetic uptake of changes in physiological variables and of breathing systems. *British Journal of Anaesthesia* 1989; 63: 633P-634P.
11. Gao F, Mapleson WW, Vickers MD. Effect of sub-anaesthetic infusions of propofol on peak velocity of saccadic eye movements. *European Journal of Anaesthesiology* 1991; 8: 267-276.
12. Marshall RW, Richens A. An IBM-based system for the generation collection and analysis of saccadic and smooth pursuit eye movements. *British Journal of Clinical Pharmacology* 1989; 28: 752P-753P.
13. Davies OL, Goldsmith PL. Analysis of variance. In: *Statistical Methods in Research and Production with Special Reference to the Chemical Industry*, 4th Ed. London: Longman Group Limited, 1977; 121-177.

ATTENUATION OF THE PRESSOR RESPONSE TO TRACHEAL INTUBATION BY MAGNESIUM SULPHATE WITH AND WITHOUT ALFENTANIL IN HYPERTENSIVE PROTEINURIC PATIENTS UNDERGOING CAESAREAN SECTION

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SUMMARY

The pressor response to tracheal intubation is known to be exaggerated in patients with gestational proteinuric hypertension (GPH). We have studied the effect of pretreatment with magnesium sulphate 40 mg kg⁻¹ or 30 mg kg⁻¹ with alfentanil 7.5 µg kg⁻¹ on this pressor response in 38 patients with moderate to severe GPH. The magnesium-alfentanil combination produced better control of arterial pressure and heart rate than magnesium alone, although both techniques provided good cardiovascular control. There was no significant difference in fetal outcome between groups. Both pretreatment methods produced satisfactory control of catecholamine release.

KEY WORDS

Anaesthesia: obstetric. Complications: gestational hypertension. Intubation, tracheal: alfentanil, pressor response, magnesium sulphate.

There is a marked pressor response to tracheal intubation in the hypertensive pregnant patient, with increases in systemic and pulmonary arterial pressures and pulmonary capillary wedge pressure [1, 2]. There is also an associated increase in intracranial pressure and in the risks of cerebral haemorrhage and cardiac failure with pulmonary oedema; as a result, morbidity and mortality in both mother and child are increased [3]. There have been several attempts to attenuate these haemodynamic responses using high- and low-dose opioids, adrenoceptor blockers, vasodilators, and topical and i.v. anaesthetics. None of these

techniques appears to be entirely satisfactory for patients with gestational proteinuric hypertension (GPH) [4]. Alfentanil appears to be the most promising of the opioids, with its rapid onset and short duration of action [5], and has been shown, at a dose of 10 µg kg⁻¹, to obtund the pressor response whilst producing minimal fetal depression in normal pregnancies [6]. Caution is advocated regarding possible detrimental effects on the fetus [7] and the mother [8].

Magnesium sulphate (MgSO₄) has been shown not only to inhibit catecholamine release [9] but also to control the pressor response to tracheal intubation [10]. Its role in the management of GPH has been established for some time [11], and it has been shown to antagonize the action of several vasoconstrictor substances in pregnant ewes [12]. We have shown previously [13] that both alfentanil 10 µg kg⁻¹ and MgSO₄ 40 mg kg⁻¹ produced adequate control of arterial pressure at tracheal intubation in GPH, but there were disadvantages with both agents. In the alfentanil-treated group, marked neonatal depression occurred and 25% of patients had failure of adequate control of arterial pressure (defined as a systolic arterial pressure > 180 mm Hg sustained for 2 min or more after intubation). Good control of arterial pressure was achieved in all but two patients in the MgSO₄ group, but with significant tachycardia. As the two drugs act via different

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mechanisms, it is possible that a combination of both drugs in reduced doses may produce the benefits of both, with fewer side effects. As MgSO_4 had proved the best of the agents tested previously, we have compared the effects of MgSO_4 with a combination of MgSO_4 and alfentanil on the cardiovascular responses to tracheal intubation in patients with severe GPH requiring Caesarean section under general anaesthesia. As both magnesium [10] and alfentanil [14] have been shown independently to inhibit the release of catecholamines at the time of tracheal intubation, it was considered that the combination could prove effective, not only in reducing the hypertensive response to intubation, but also in inhibiting release of catecholamines. The dose of the two agents was chosen after a preliminary investigation in non-pregnant subjects showed that magnesium 30 mg kg^{-1} with alfentanil $5 \mu\text{g kg}^{-1}$ was not significantly better than alfentanil alone.

PATIENTS AND METHODS

The study was approved by the Human Ethics Committee of the University of Cape Town, and written informed consent was obtained from all participants. Entry and exclusion criteria for the study were identical to those used for our previous investigation, as were pre-anaesthetic management regimens [13]. Patients were allocated randomly to one of two groups: group 1 received MgSO_4 40 mg kg^{-1} and group 2 received MgSO_4 30 mg kg^{-1} + alfentanil $7.5 \mu\text{g kg}^{-1}$.

On arrival of the patient in the operating theatre suite, an indwelling cannula was inserted under local anaesthetic into a vein in the antecubital fossa for blood sampling, on the arm opposite to that in which the i.v. drip was sited. At this stage, blood was taken for baseline estimations. This sample was analysed for serum urea and electrolytes, calcium, magnesium and catecholamine concentrations. All subsequent maternal samples were analysed for magnesium, alfentanil and catecholamine concentrations. Catecholamine concentrations were measured by electrochemical detection after separation with reverse phase HPLC using dihydrobenzylamine as internal standard [15]. The coefficient of variation was 7.9% for noradrenaline and 8.7% for adrenaline, and the limit of sensitivity was 10 pg ml^{-1} . Alfentanil concentrations were measured by gas chromatography. Continuous, non-invasive

arterial pressure monitoring and anaesthetic techniques were similar to those described previously [13].

A second blood sample was obtained 1 min after completion of laryngoscopy and intubation, taken as the time when the cuff of the tracheal tube was inflated. Anaesthesia was maintained for 5 min before the start of surgery with 50% nitrous oxide and 0.5% halothane in oxygen with ventilation adjusted to ensure normocapnia, during which time arterial pressure was measured continuously. Neuromuscular block was maintained with an infusion of suxamethonium $4\text{--}8 \text{ mg min}^{-1}$ and neuromuscular function monitored using a nerve stimulator.

At the end of the 5 min monitoring period, during which time the patient had been cleaned and draped, another venous blood sample was obtained. Surgery then commenced and the times from skin incision to delivery, and uterine incision to delivery were noted. After delivery of the infant, when the rectus muscle was being sutured, the suxamethonium infusion was discontinued and at the onset of spontaneous breathing, another sample of maternal blood was obtained.

Cardiovascular responses to surgery were noted. At delivery of the infant, cord blood was sampled for serum concentrations of magnesium and alfentanil where appropriate, and for fetal acid-base status. After delivery, neonates were scored on the Apgar system at 1 and 5 min, by a paediatrician who was blinded to the study drug given. The paediatrician also recorded what resuscitative measures had been necessary, including the use of naloxone and the response to this drug.

Statistical analysis was performed using Statgraphics (Version 4.0) statistical package running under MS-DOS (version 3.3) on an IBM-compatible AT personal computer. Between-group comparisons were performed using Student's *t* test, Wilcoxon rank sum and Fisher's Exact tests where appropriate. The sample size was determined as the smallest necessary to detect a 15-mm Hg between-group difference within the anticipated systolic arterial pressure range with an estimated SD of 20 mm Hg for each group ($\alpha = 0.05$; $\beta = 0.1$). Within-group comparisons were performed using analysis of variance for repeated measures with the use of 95% confidence intervals to identify significantly different samples. All maternal data were grouped and analysed by regression analysis for association between the

TABLE I. Maternal characteristics and arterial pressure on admission (mean (SD)). Emerg. = Emergency procedure; Elect. = elective procedure. No significant differences between groups

Group	Age (yr)	Weight (kg)	Gestational age (weeks)	Emerg. (No.)	Elect. (No.)	Arterial pressure (mm Hg)		
						Systolic	Diastolic	Mean
1 (n = 19)	25.6 (6.7)	72.9 (15.3)	32.5 (4.1)	19	0	158.9 (21.1)	108.4 (14.8)	123.7 (17.6)
2 (n = 19)	26.3 (4.9)	77.6 (13.9)	32.1 (3.9)	18	1	167.9 (22.7)	108.9 (13.6)	132.9 (21.7)

TABLE II. Preoperative medication used in the 12 h before surgery to control the symptomatology of GPH in the two groups, and steady state arterial pressures in the operating room (mean (SD)). No significant between-group differences

Group	Nil (No.)	MgSO ₄ (No.)	Aldomet (No.)	Nifedipine (No.)	β-Blocker (No.)	Hydralazine (No.)	AP (mg Hg)		
							Systolic	Diastolic	Mean
1 (n = 19)	3	11	3	6	0	5	181.6 (19.8)	110.5 (12.5)	142.2 (18.0)
2 (n = 19)	4	9	6	5	2	4	174.1 (24.9)	105.2 (9.9)	133.0 (17.5)

TABLE III. Magnesium and catecholamine concentrations at various times (mean (SD)). No significant differences between groups

Group	Baseline		After intubation		Before incision		After delivery	
	1	2	1	2	1	2	1	2
Magnesium (mmol litre ⁻¹)	1.39 (0.43)	1.31 (0.36)	2.41 (0.80)	2.19 (0.50)			1.92 (0.56)	1.64 (0.35)
Noradrenaline (pg ml ⁻¹)	802 (646)	777 (475)	636 (434)	464 (389)	570 (473)	567 (300)	715 (495)	728 (412)
Adrenaline (pg ml ⁻¹)	263 (243)	155 (170)	261 (291)	176 (210)	187 (278)	192 (207)	423 (385)	375 (347)

severity of cardiovascular responses and maternal age, parity and initial diastolic pressure. The null hypothesis was rejected at $P < 0.05$.

RESULTS

Subjects in both groups were well matched in respect of age, weight, gestational age and cardiovascular variables (table I) and there were no significant differences in routine biochemical variables between the groups.

After arterial pressure had been stabilized in the operating theatre, the cardiovascular data of the two groups were not significantly different (table II) and the use of antihypertensive medications within 12 h of surgery was basically similar in both groups.

Only one patient suffered a convulsion before admission to the study and she was allocated to group 2. Of the 20 patients who had received MgSO₄ before entry to the study, one patient had a serum concentration of magnesium within the normal range (0.75–1.0 mmol litre⁻¹), and only one had a value generally regarded as therapeutic (> 2 mmol litre⁻¹). In the remainder, the serum concentrations of magnesium varied between 1 and 2 mmol litre⁻¹ (table III). There was no statistically or clinically significant difference between the values in the two groups, despite the different bolus doses of MgSO₄. The greatest serum concentration of magnesium recorded after administration of MgSO₄ was 3.65 mmol litre⁻¹ and after delivery the greatest value recorded was 2.35 mmol litre⁻¹. The mean serum concentration

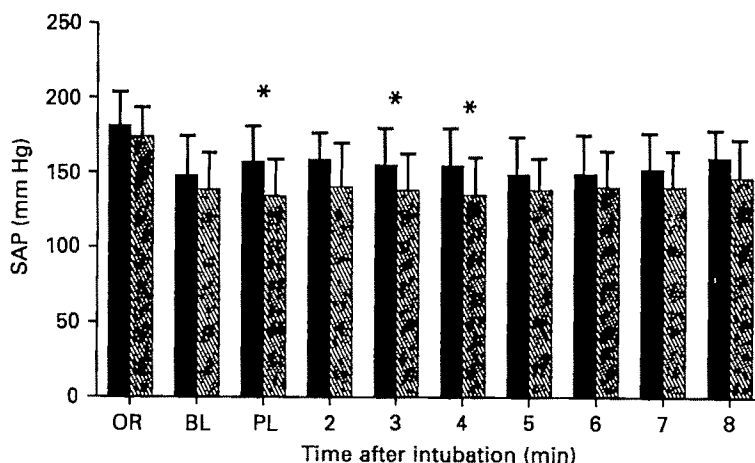


FIG. 1. Mean (SD) systolic arterial pressures (SAP) in the magnesium (■) and magnesium plus alfentanil (▨) groups. Times refer to time from induction and administration of the study drug. OR = Stable value with the patient settled in theatre; BL = value before laryngoscopy, after induction and administration of study drug; PL = peak values during or after laryngoscopy and intubation. *Statistically significant differences between groups ($P < 0.05$). Systolic pressure was significantly different from baseline in both groups at all shown times after induction.

of magnesium at the end of the procedure was less than that associated with neuromuscular impairment (table III), and no difficulties were experienced in re-establishing neuromuscular function at the end of the procedure.

Systolic, diastolic and mean arterial pressures decreased significantly after induction in both groups, and there was no significant difference in the magnitude of the change in the two groups. There was no statistically significant mean increase in arterial pressure at tracheal intubation, but there was significantly better control of systolic arterial pressure (SAP) in group 2 mothers at laryngoscopy and at 3 and 4 min afterwards (fig. 1). Systolic arterial pressure remained less than baseline from induction until the onset of surgery in both groups. Similar trends occurred in mean and diastolic arterial pressures, with significant between-group differences at the same times as for systolic pressure changes. There were no serious hypotensive episodes; the least mean arterial pressure was 70 mm Hg, in a group 2 subject at 2 min after intubation. Arterial pressure control was also analysed using our previous criteria [13] for inadequate control, defined as an increase in systolic arterial pressure to > 180 mm Hg for 2 min or more. Satisfactory arterial pressure control was achieved in both groups, with only one mother in group 2 compared with three in group 1 showing inadequate

control (ns between groups). Only one patient (in group 1) showed an increase in systolic pressure to a value greater than her initial pressure before induction. There was no correlation between the severity of the hypertensive response to tracheal intubation and patient age, parity or initial diastolic arterial pressure.

Heart rates increased significantly after induction in both groups, but absolute values and the magnitude of the increase with induction were significantly less in group 2 (fig. 2). Heart rate remained greater than before induction until 4 min after tracheal intubation in group 1, but in group 2 heart rate was significantly different from baseline only immediately after intubation. Heart rate did not increase further in either group during or after laryngoscopy, but heart rate was significantly less in group 2 than in group 1 immediately after laryngoscopy had been completed. Consequently, the rate-pressure products were significantly smaller in group 2 during this period. There were no arrhythmias in either group. Three difficult intubations were encountered, with laryngoscopy to intubation times of 25 s or greater. These were all in group 2 and not associated with remarkable changes in arterial pressure.

The mean baseline serum concentrations of catecholamines were increased in both groups (table III), although there was considerable

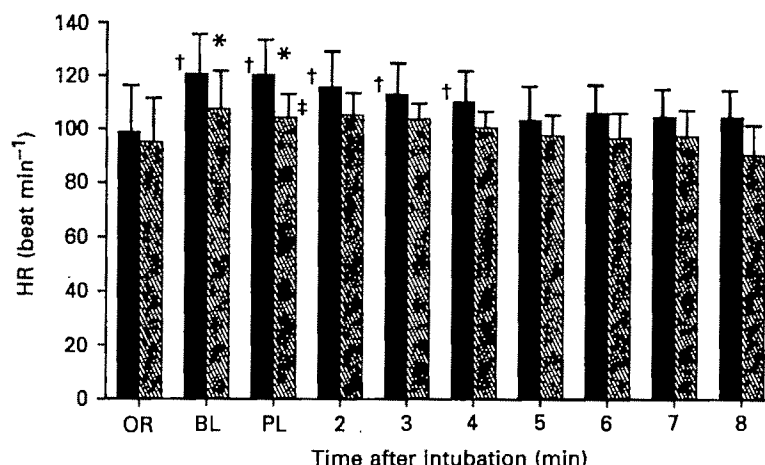


FIG. 2. Mean (SD) heart rates (HR) in the magnesium (■) and magnesium plus alfentanil (▨) groups at the times described in figure 1. * Statistically significant differences between groups ($P < 0.05$); † group 1 significantly different from baseline; ‡ group 2 significantly different from baseline.

TABLE IV. Neonatal data (mean (SD) or † median (range)). Tube? = Number of neonates requiring tracheal intubation. No statistically significant differences between groups

Group	Birth wt (g)	Fetal pH	Mg ²⁺ (mmol litre ⁻¹)	Apgar score†		Tube? (No.)
				1 min	5 min	
1 (n = 19)	1632 (759.7)	7.21 (0.1)	2.0 (0.8)	6 (1-9)	9 (4-10)	4
2 (n = 19)	1567.5 (678.6)	7.23 (0.1)	1.5 (0.4)	6 (1-9)	8 (1-10)	7

variability in the data. Thirteen patients in group 1 and 15 in group 2 had serum concentrations of catecholamines greater than the normal range for our laboratory (adrenaline 10–80 pg ml⁻¹, noradrenaline 200–400 pg ml⁻¹) before induction of anaesthesia. However, there were no significant differences in absolute values, or in the changes in adrenaline or noradrenaline concentrations between groups 1 and 2 at any time. It is of particular interest that there was no overall increase in the concentration of each catecholamine at tracheal intubation. There was also no correlation between arterial pressure changes and changes in serum concentrations of catecholamines. However, four patients in each group showed increases in their serum concentrations of noradrenaline after tracheal intubation, and these included the worst controlled patients in each group. Both groups showed similar increases in serum concentrations of catecholamines towards the end of the procedure when the plasma

concentrations of both magnesium and alfentanil were declining, and tracheal extubation was associated with significant increases in arterial pressure and heart rate.

Maternal mean serum concentrations of alfentanil in group 2 mothers 1 min after tracheal intubation and after delivery were 62.8 (SD 20.6) ng ml⁻¹ and 14.6 (5.4) ng ml⁻¹, respectively, and the concentration in the mixed cord blood of their infants was 8.3 (4.9) ng ml⁻¹. There was no correlation between initial maternal alfentanil concentrations and umbilical concentrations, although there was a weak correlation ($r = 0.41$) between post-delivery maternal concentrations and those in the umbilical artery. There was no significant difference between groups in the use of, or response to, naloxone in the neonates.

The values of the various neonatal variables recorded are shown in table IV. There was no statistically significant difference between the groups in any of the variables. There was no

correlation between any of the alfentanil or magnesium measurements and any measurement of neonatal well-being.

DISCUSSION

In our previous study [13], we concluded that MgSO_4 was superior to either lignocaine or alfentanil for attenuation of the pressor response to tracheal intubation. In this study, we have confirmed that MgSO_4 was highly satisfactory for this purpose, but it appeared that the combination of MgSO_4 and alfentanil, both in reduced doses, was superior to the use of each agent alone, in terms of both maternal arterial pressure control and changes in heart rate. This combination did not appear to have any significant disadvantage for these compromised fetuses. There was no evidence that the reduction in arterial pressure compromised the fetus, and it has been shown that magnesium-induced hypotension does not reduce uterine blood flow [16].

These results show better cardiovascular control than those reported by Rout and Rocke [17] using either fentanyl or alfentanil in combination with droperidol and lignocaine. They found significant increases in both systolic and diastolic pressures and heart rate after tracheal intubation. However, they chose a more severely ill group of patients in that all their subjects were older than 25 yr, and all had diastolic arterial pressures > 110 mm Hg whereas, in our study, 13 of the patients were younger than 25 yr and nine had diastolic pressures between 90 and 110 mm Hg. We were unable to find any evidence that patient age, resting diastolic arterial pressure or parity had any influence on the severity of the response, in contradistinction to other reports [2, 3, 17].

Dann, Hutchinson and Cartwright [7] reported the absence of neonatal effects of maternally administered alfentanil, and hypothesized that the effect of alfentanil on the neonate would be minimal because of its short half-life. This study has confirmed that, in the hypertensive, proteinuric, pregnant patient, rapid elimination of alfentanil occurred, and that very low fetal concentrations of alfentanil may be anticipated. We did not measure free alfentanil concentrations, but it seems likely that these premature neonates had less plasma protein binding of alfentanil than normal neonates, who also have a smaller percentage of alfentanil binding than adults [8]. For any given concentration of alfentanil, a greater

effect may therefore be anticipated in the premature neonate. Redfern and colleagues [8] reported severe depression in a neonate with a total plasma concentration of alfentanil 22.4 ng ml^{-1} which was considerably greater than the concentrations observed in our neonates. The smaller concentrations measured in the neonates in our study presumably account for the apparent lack of alfentanil-induced depression. However, the margin of safety appears to be rather small, and this may explain the significant depression which we observed in our previous study with only a slightly greater dose of alfentanil ($10 \mu\text{g kg}^{-1}$) [13].

It is interesting that there were no inter-group differences in catecholamine concentrations. There was no mean increase in catecholamine concentrations in either group, which contrasts with reports of 21% [18] and 28% [19] increases in noradrenaline in normal patients and a 33% increase in GPH patients [19]. The lesser arterial pressures and heart rates in group 2 were clearly not attributable to differences in release of catecholamines. This is not entirely surprising, as the concentrations of circulating noradrenaline required to exert measurable haemodynamic effects are in the range $1500\text{--}2000 \text{ pg ml}^{-1}$ [20], values which were observed in only one patient in this study. Presumably, therefore, the small increases in arterial pressure occurring after intubation in both groups were the result of sympathetic nerve stimulation. Mean plasma concentrations of adrenaline were unchanged in both groups after tracheal intubation, and the lower heart rate seen in group 2 was presumably caused by the direct effect of alfentanil on heart rate.

ACKNOWLEDGEMENT

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REFERENCES

1. Hodgkinson R, Hussain FJ, Hayashi RH. Systemic and pulmonary blood pressure during Caesarean section in parturients with gestational hypertension. *Canadian Anaesthetists Society Journal* 1980; 27: 389–393.
2. Connell H, Dagleish JG, Downing JW. General anaesthesia in mothers with severe pre-eclampsia/eclampsia. *British Journal of Anaesthesia* 1987; 59: 1375–1380.
3. Lawes EG, Downing JW, Duncan PW, Bland B, Lavies N, Gane GEC. Fentanyl-droperidol supplementation of rapid sequence induction in the presence of severe pregnancy-induced and pregnancy-aggravated hypertension. *British Journal of Anaesthesia* 1987; 59: 1381–1391.
4. Morison DH. Anaesthesia and pre-eclampsia. *Canadian Journal of Anaesthesia* 1987; 34: 415–422.

5. Ralston DH, Shnider SM. The fetal and neonatal effects of regional anesthesia in obstetrics. *Anesthesiology* 1978; 48: 34-38.
6. Black TE, Kay B, Healy TEJ. Reducing the haemodynamic responses to laryngoscopy and intubation. A comparison of alfentanil with fentanyl. *Anaesthesia* 1984; 39: 883-887.
7. Dann WL, Hutchinson A, Cartwright DP. Maternal and neonatal responses to alfentanil administered before induction. *British Journal of Anaesthesia* 1987; 59: 1392-1396.
8. Redfern N, Bower S, Bullock RE, Hull CJ. Alfentanil for Caesarean section complicated by severe aortic stenosis. *British Journal of Anaesthesia* 1987; 59: 1309-1312.
9. Lishajko F. Releasing effect of calcium and phosphate on catecholamines, ATP, and protein from chromaffin cell granules. *Acta Physiologica Scandinavica* 1970; 79: 575-585.
10. James MFM, Beer RE, Esser JD. Intravenous magnesium sulfate inhibits catecholamine release associated with tracheal intubation. *Anesthesia and Analgesia* 1989; 68: 772-776.
11. Pritchard JA, Cunningham G, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. *American Journal of Obstetrics and Gynecology* 1984; 148: 951-963.
12. Sipes S, Chestnut D, Vincent R, Weiner C. Does magnesium sulfate alter the maternal cardiovascular response to vasopressor agents in gravid ewes? *Anesthesiology* 1990; 73: A969.
13. Allen RW, James MFM, Uys PC. Attenuation of the pressor response to intubation on hypertensive proteinuric patients by lignocaine, alfentanil and magnesium sulphate. *British Journal of Anaesthesia* 1991; 66: 216-223.
14. Crawford DC, Fell D, Achola KJ, Smith G. Effects of alfentanil on the pressor and catecholamine responses to tracheal intubation. *British Journal of Anaesthesia* 1987; 59: 707-712.
15. Weicker H, Feraudi N, Haegle H, Pluto R. Electrochemical detection of catecholamines in urine and plasma after separation with HPLC. *Clinica Chimica Acta* 1984; 141: 17-25.
16. Vincent RD, Chestnut DH, Sipes SL, Weiner CP, DeBruyn CS, Bleuer SA. Magnesium decreases maternal blood pressure but not uterine blood flow during epidural anesthesia in gravid ewes. *Anesthesiology* 1991; 74: 77-82.
17. Rout CC, Locke DA. Effects of alfentanil and fentanyl on induction of anaesthesia in patients with severe pregnancy-induced hypertension. *British Journal of Anaesthesia* 1990; 65: 468-474.
18. Shnider SM, Abboud T, Levinson G, Wright RG, Kim S, Henriksen E, Hughes SC, Roizen MF, Johnson J. General anesthesia for cesarean section: maternal and fetal norepinephrine levels and neonatal neurobehavioral status. *Anesthesiology* 1980; 53: S302.
19. Lavies NG, Meiklejohn BH, May AE, Achola KJ, Fell D. Hypertensive and catecholamine response to intubation in patients with pregnancy-induced hypertension. *British Journal of Anaesthesia* 1989; 63: 429-434.
20. Cryer PE. Physiology and pathophysiology of the human sympatho-adrenal neuroendocrine system. *New England Journal of Medicine* 1980; 303: 436-444.

EFFECT OF SUBLINGUAL BUPRENORPHINE ON GASTRIC EMPTYING OF A LIQUID MEAL

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AND M. C. MUSHAMBI

SUMMARY

The effect of buprenorphine 0.2 mg sublingually on gastric emptying of a liquid meal in 10 volunteers was compared with placebo. Gastric emptying was measured by applied potential tomography and was delayed significantly by buprenorphine ($P < 0.001$).

KEY WORDS

Analgesics; buprenorphine. Gastrointestinal tract: gastric emptying.

Pulmonary aspiration of gastric contents is an important cause of anaesthetic morbidity and mortality [1, 2]. Delay in gastric emptying may increase the risk of regurgitation and also delay absorption of drugs administered orally.

Buprenorphine is a partial opioid agonist used in the treatment of acute and chronic pain [3, 4]. Delayed absorption of oral paracetamol, associated presumably with delayed gastric emptying, has been demonstrated in volunteers after i.v. administration of buprenorphine $4 \mu\text{g kg}^{-1}$ [5]. However, buprenorphine is usually administered sublingually and not as an i.v. bolus. Gastric emptying after sublingual administration of buprenorphine has not been measured.

Applied potential tomography (APT) can be used to measure directly the rate of emptying of solid and liquid meals from the stomach and correlates well with scintigraphic techniques [6]. We have used APT to measure the effect of sublingual administration of buprenorphine 0.2 mg on gastric emptying of a liquid meal.

using electrodes placed around the epigastrium. After ingestion of a test meal, changes in resistivity are measured and a profile of gastric emptying is generated. Sixteen electrodes are placed around the abdomen at the level of the eighth costal cartilage; this level corresponds with the gastric fundus or body [6]. An alternating current (1 mA, 50 kHz) is passed between two adjacent electrodes and the potential differences between the remaining pairs are measured. During the measurement cycle, each pair of electrodes acts in sequence

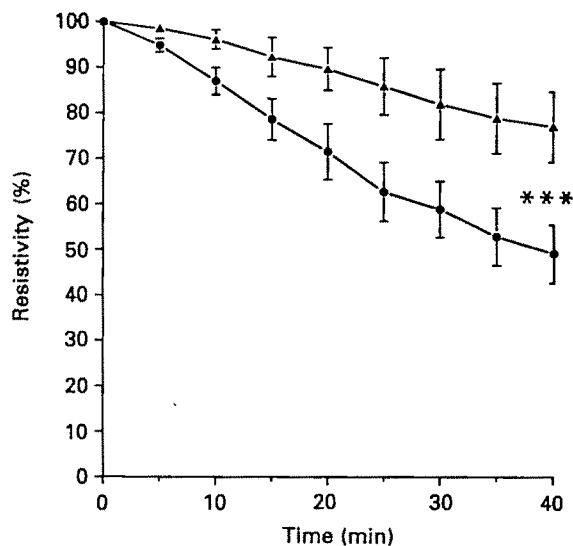


FIG. 1. Mean (SEM) percentage resistivity remaining. Δ — Δ = buprenorphine; $\bullet$ — $\bullet$ = control. *** $P < 0.001$. (MANOVA for repeated measures).

PATIENTS AND METHODS

Applied potential tomography

Applied potential tomography generates tomographic images of the resistivity of gastric contents

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as drive electrodes and a total of 208 measurements are made in 100 ms. One hundred and fifty cycles are added together in order to form one data set, enabling the effect of respiratory movements to be averaged out. Measurements are made before, and at 1-min intervals after, the test meal.

Data are stored on disc by a Nimbus RM computer and back projected against the initial preprandial data. A cross-sectional image of the change in resistivity is produced which incorporates changes in resistivity 4 cm above and below the plane of the electrodes. The area on the image representing the stomach is visible clearly and changes in resistivity with time within this area are calculated.

Gastric secretion of hydrogen ions after ingestion of a test meal may affect resistivity measurements significantly. Therefore, it is necessary to administer a histamine type-2-receptor antagonist before measurement of gastric emptying with APT. Cimetidine does not affect the rate of gastric emptying [7, 8] and was used in this study.

Study design

After obtaining written informed consent, we investigated 10 healthy non-smoking volunteers in a double-blind, placebo-controlled study which was approved by the local Ethics Committee. Each subject was studied on two occasions at least 2 days apart.

After an overnight fast, cimetidine 800 mg was administered orally, followed by buprenorphine 0.2 mg or placebo sublingually 1.5 h later. After a further 2 h, subjects adopted a semisupine position at 45°. A liquid meal of beef consommé soup 500 ml (Campbell's) was given and gastric emptying measured. Data were collected for 40 min and the percentage of total resistivity remaining at the end of the study period and the decrease in resistivity with time within the stomach were recorded.

Data were analysed using paired Student's *t* test and MANOVA for repeated measures after testing the data for normality with the Kolmogorov-Smirnov goodness of fit test.

RESULTS

All 10 volunteers (five male) completed the study. Mean age was 30.3 yr (range 26–35 yr) and mean weight 62.9 (SD 7.0) kg.

TABLE I. Resistivity (%) remaining after 40 min.
*** $P < 0.001$

Subject No.	Placebo (%)		Buprenorphine (%)
1	54		75
2	14		56
3	15		36
4	48		85
5	50		43
6	77		100
7	66		92
8	50		93
9	61		91
10	55		100
Mean	49.0	***	77.1
SEM	6.4		7.5

Figure 1 shows the mean (SEM) percentage of resistivity that remained over time after placebo compared with buprenorphine, and the percentage resistivity remaining after 40 min in each volunteer is shown in table I. Mean (SEM) values were significantly less after placebo (49 (6.4)%) compared with buprenorphine (77 (7.5)%) ($P < 0.001$).

Nausea occurred in three subjects after buprenorphine but no subject vomited during the study period.

DISCUSSION

The recommended initial dose of buprenorphine for sublingual administration is 0.2–0.4 mg [9]. We have examined the effect of buprenorphine 0.2 mg sublingually on gastric emptying of a liquid meal in healthy volunteers. In five volunteers, there was almost complete cessation of gastric emptying during the study period (less than 10% emptying); moderate delay occurred in four subjects and gastric emptying was unchanged in one volunteer.

The effects of buprenorphine on gastric emptying have been investigated previously in only one study [5]. I.v. buprenorphine 4 $\mu\text{g kg}^{-1}$ caused delay in absorption of paracetamol in seven of eight volunteers. The remaining volunteer was excluded because of vomiting during the study. The results of the present study are consistent with these findings, despite the fact that considerably greater peak plasma concentrations of buprenorphine are achieved after i.v. administration compared with the sublingual route [10].

Time to peak concentration after sublingual administration of buprenorphine varies from

30 min to more than 3 h (mean 150 min) [10]. In the present study, data collection commenced 2 h after buprenorphine administration and it is likely that peak concentrations were not achieved in some subjects during this period. Therefore, the effect of buprenorphine on gastric emptying may have been underestimated in the present study. Pharmacokinetic interaction between cimetidine and buprenorphine may have occurred in this single-dose study, but this is unlikely. Buprenorphine is excreted mainly unchanged in the faeces [11] and we have been unable to find any reported interactions.

In conclusion, acute administration of buprenorphine 0.2 mg sublingually is likely to cause marked delay in gastric emptying in most patients. This may influence the absorption of orally administered drugs and increase the risk of regurgitation.

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REFERENCES

1. Department of Health and Social Security. *Report on Confidential Enquiries into Maternal Deaths in England and Wales*. London: Her Majesty's Stationary Office, 1986.
2. Lunn JN, Mushin WW. *Mortality Associated with Anaesthesia*. London: Nuffield Provincial Hospital Trust, 1982.
3. Edge WG, Cooper GM, Morgan M. Analgesic effects of sublingual buprenorphine. *Anaesthesia* 1979; **34**: 463-467.
4. Adriaensen H, Van der Walle. Clinical use of buprenorphine in chronic administration. *Acta Anaesthesiologica Belgica* 1976; **27**: 187-191.
5. Adelhoff B, Petring OU, Ibsen M, Byrnum J, Poulsen HE. Buprenorphine delays drug absorption and gastric emptying in man. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 599-601.
6. Avill R, Mangnall YF, Bird NC, Brown BH, Barber DC, Seagar AD, Johnson AG, Read NW. Applied potential tomography; a new noninvasive technique for measuring gastric emptying. *Gastroenterology* 1987; **92**: 1019-1026.
7. Scarpignato C, Bertaccini G, Zimbaro G, Vitulo F. Ranitidine delays gastric emptying of solids in man. *British Journal of Clinical Pharmacology* 1982; **13**: 252-253.
8. Jonderko K. Influence of oral cimetidine and ranitidine on gastric emptying in active duodenal ulcer. *Journal of Clinical Gastroenterology* 1988; **10**: 143-149.
9. *British National Formulary*, 21st Edn. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1991; 163.
10. Bullingham RES, McQuay HJ, Dwyer D, Allen MC, Moore RA. Sublingual buprenorphine used postoperatively: clinical observations and preliminary pharmacokinetic analysis. *British Journal of Clinical Pharmacology* 1981; **12**: 117-122.
11. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th Edn. New York: Pergamon, 1990; 513-514.

GENERAL ANAESTHETICS INDUCE ONLY HISTAMINE RELEASE SELECTIVELY FROM HUMAN MAST CELLS

C. STELLATO, V. CASOLARO, A. CICCARELLI, P. MASTRONARDI, B. MAZZARELLA AND G. MARONE

SUMMARY

We have examined the *in vitro* effects of increasing concentrations of propofol (5–70 $\mu\text{g ml}^{-1}$), ketamine (10^{-6} – 10^{-3} mol litre $^{-1}$) and thiopentone (10^{-5} – 8×10^{-4} mol litre $^{-1}$) on the release of preformed histamine and *de novo* synthesized mediators (peptide leukotriene C_4 (LTC_4) or prostaglandin D_2 (PGD_2)) from human basophils and mast cells isolated from lung parenchyma and skin tissue and from heart fragments. Propofol, ketamine and thiopentone failed to induce the release of histamine and *de novo* synthesis of LTC_4 from basophils. Propofol induced histamine release from lung (mean 8.6 (SEM 1.6) %) and skin mast cells (3.8 (1.5) %), but not from heart mast cells. Ketamine caused release of histamine from lung (6.2 (0.9) %) and skin mast cells (2.5 (1.5) %). Thiopentone caused a small amount of histamine release from lung mast cells (3.1 (1.2) %). Propofol, ketamine and thiopentone did not induce *de novo* synthesis of PGD_2 and LTC_4 from lung and skin mast cells. These results demonstrate that general anaesthetics induce only histamine release selectively from human mast cells.

KEY WORDS

Anaesthetics, intravenous: propofol, ketamine, thiopentone. Allergy: anaphylaxis, histamine.

The number of anaphylactoid reactions reported during general anaesthesia is increasing [1]. The estimated incidence of anaphylactic/anaphylactoid reactions during general anaesthesia is approximately 0.6 % (0.05 % fatal) [2, 3]. Although neuromuscular blockers are the drugs implicated most frequently in these reactions [4], general anaesthetic drugs also may induce anaphylactoid reactions [5–9].

The mechanisms of adverse reactions to general anaesthetics are complex [10]. However, whatever the mechanism(s), the resulting clinical manifestations are attributed commonly to histamine release by human mast cells and basophils [6, 7, 11]. This is supported by the findings that general anaesthetics cause histamine release *in vitro* [12] and *in vivo* [6, 7] and that administration of histamine reproduces most of the metabolic and haemodynamic effects observed during anaphylactic/anaphylactoid reactions [13–15].

An early commercial preparation of propofol was found to produce a high incidence of adverse reactions [16], presumably as a result of the histamine releasing capacity of the solubilizing agent, Cremophor EL [7, 17]. Propofol was therefore re-formulated, solubilized in a soya bean oil emulsion. However, the *in vivo* administration of propofol may produce skin flushing and a transient increase in plasma concentrations of histamine [17]. Despite these *in vivo* observations, the capacity of propofol to induce *in vitro* the release of histamine from human basophils and mast cells isolated from different anatomical sites has never been studied.

Techniques are now available to isolate large numbers of mast cells from human lung parenchyma [18], skin tissue [19] and human heart fragments [20]. These techniques have led to the demonstration that human basophils and mast cells isolated from different anatomical sites vary markedly as to their morphological, bio-

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chemical and functional responses [18, 21–23]. Heterogeneity among these cells has been demonstrated with respect to the releasing activity of various stimuli and the release of different preformed histamine and *de novo* synthesized mediators (peptide leukotriene C_4 (LTC_4) and prostaglandin D_2 (PGD_2)) [19, 24].

Preliminary evidence suggests that human basophils and mast cells may also vary in their histamine releasing capacity when challenged with general anaesthetics. For example, thiopentone activates skin mast cells [12] but not human basophils. It should be emphasized that previous studies have focused on the histamine releasing capacity of anaesthetic drugs, but have not evaluated their possible effects on the *de novo* synthesis of chemical mediators.

We have investigated the ability of three i.v. general anaesthetic agents used commonly in clinical practice (propofol, ketamine and thiopentone) to induce the release of preformed and *de novo* synthesized mediators from human basophils and mast cells isolated from skin tissues, lung parenchyma and heart fragments.

MATERIALS AND METHODS

Reagents

The following reagents were used: Dextran 70 (Pharmacia Fine Chemicals, Uppsala, Sweden); piperazine - N, N' - bis (2 - ethanesulfonic acid) (PIPES), elastase type I, hyaluronidase, chymopapain, collagenase, synthetic LTC_4 and PGD_2 (Sigma Chemical Co., St Louis, MO); Hank's balanced salt solution (HBSS), fetal calf serum (FCS) (Gibco, Grand Island, NY); A23187, DNAase, pronase (Calbiochem, La Jolla, CA); RPMI 1640 with Hepes buffer 25 mmol litre⁻¹, Eagle's minimum essential medium (MEM) (Flow Laboratories, Irvine, Scotland); ^3H - LTC_4 (39.3 Ci mmol⁻¹) and ^3H - PGD_2 (210 Ci mmol⁻¹) (New England Nuclear, Boston, MA). The following i.v. anaesthetic agents were used: propofol (Imperial Chemical Industries PLC, Macclesfield, U.K.), ketamine (Parke-Davis S.p.A., Milan, Italy) and thiopentone (Abbott S.p.A., Latina, Italy).

Histamine release from human basophils

After informed consent was obtained from all subjects, approximately 50 ml of blood was drawn into a final concentration of EDTA

0.008 mol litre⁻¹ and 1.1 % Dextran 70 [25]. The procedure for the isolation of peripheral blood basophils and the *in vitro* mediator release have been described in detail elsewhere [24, 25]. The cell-free supernatant was assayed for histamine with an automated fluorimetric technique [26]. The net percentage release was calculated by subtracting the histamine released spontaneously from the unstimulated aliquots (mean 2.8 (SEM 0.8) %) from the total histamine released from cell aliquots lysed with 2 % perchloric acid [24]. The difference between replicate histamine measurements was less than 10 %.

Purification of human skin mast cells

Skin was obtained from either mastectomies for breast cancer or elective cosmetic surgery procedures. General anaesthesia in these patients was performed using the following drugs: thiopentone, pancuronium, atropine, fentanyl, enflurane or isoflurane.

Tissue was placed immediately in Eagle's MEM at 4 °C and used within 1 h. The skin was separated from the subcutaneous fat by blunt dissection and fragments were washed twice in calcium- and magnesium-free HBSS (CMF-HBSS) at 22 °C and incubated in a solution of CMF-HBSS containing collagenase 20 mg/g wet weight of tissue, hyaluronidase 5 mg/g wet weight of tissue and DNAase 1000 u ml⁻¹ for 3 h at 37 °C under constant stirring [19, 27]. The isolated cells were separated from the partially digested tissue fragments by filtration through Nytex cloth (150- μ m pore size) and stored. The remaining tissue was digested a second time with a fresh batch of the enzymes for a further 2 h at 37 °C. The cells were separated from the tissue fragments by filtration through Nytex cloth, washed twice, combined with the cells from the first digestion, and washed again in CMF-HBSS. Yields obtained with this technique were $1-8 \times 10^5$ mast cells/g wet weight of tissue, and purities varied between 1 % and 4 %.

Purification of human lung mast cells

Human lung tissue was obtained from patients undergoing thoracotomy and lung resection, mostly for lung cancer. General anaesthesia in these patients was performed using the following drugs: droperidol plus fentanyl and atropine (premedication); droperidol plus fentanyl, thiopentone, suxamethonium and pancuronium (anaesthesia). Lung parenchymal mast cells were

isolated as described previously [18]. Yields obtained with this technique were $3-8 \times 10^5$ mast cells/g wet weight of tissue, and purities varied between 1% and 8%. Mast cells and basophils were stained with Alcian blue and counted in a Spiers-Levy eosinophil counter [18, 28].

Histamine release from human skin and lung mast cells

Aliquots of the cell suspension (0.4 ml) containing approximately 3×10^4 mast cells per tube were placed in Falcon 12×17 mm polyethylene tubes and warmed at 30 °C (skin mast cells) or 37 °C (lung mast cells); 0.2 ml of each releasing stimulus was added and incubation was continued at 30 °C (skin mast cells) or 37 °C (lung mast cells) for 30 min. Experiments with mast cells obtained from skin of adult donors were performed at 30 °C because adult skin mast cells release better at 30 °C than at 37 °C [19]. The net percentage release was calculated by subtracting the histamine released spontaneously from the unstimulated aliquots of skin (6.2 (0.7)%) and lung mast cells (12.9 (1.6)%) from the total histamine release from cell aliquots lysed with 2% perchloric acid [18, 24].

Histamine release from human heart fragments

Specimens of human right atrial appendages were obtained from patients undergoing cardiac surgery for valvular correction or substitution and aorto-coronary vein graft [20]. General anaesthesia in these patients was performed using the following drugs: thiopentone or diazepam, morphine or fentanyl, pancuronium, and nitrous oxide. None of the patients had taken dipyridamole, aspirin or any anti-inflammatory medication for at least 7 days before the operation. The procedure to evaluate the release of histamine from cardiac mast cells has been described in detail in previous publications [20, 23].

Radioimmunoassay of LTC₄ and PGD₂

LTC₄ and PGD₂ concentrations were measured by radioimmunoassay as described previously [24, 25, 29]. The rabbit anti-LTC₄ and anti-PGD₂ antisera have been characterized and their cross-reactivity for heterologous ligands described elsewhere [29, 30].

Statistical analysis

Results were expressed as mean (SEM). Statistical analysis was performed by two-way non-

parametric analysis of variance (Friedman test); multiple comparisons were performed by the extended Tukey test [31].

RESULTS

We evaluated the effects of increasing concentrations (5–70 $\mu\text{g ml}^{-1}$) of propofol [32] on histamine release from basophils and mast cells isolated from lung parenchyma and skin tissue. Propofol, in concentrations which included those reached during general anaesthesia [32], failed to induce histamine release from basophils obtained from 11 normal donors (fig. 1). We also determined the effects of propofol on the release of histamine from mast cells isolated from lung parenchyma obtained from nine donors. Propofol induced histamine release from lung mast cells in a concentration-dependent manner ($P < 0.001$). The maximum per cent histamine release caused by propofol varied between 3% and 18% (8.6 (1.6)%) ($P < 0.01$ compared with spontaneous release). In three of nine skin mast cell preparations, propofol induced the release of more than 5% of the histamine content ($P < 0.05$). The greatest concentration of propofol used induced the release of 3.8 (1.5)% of skin mast cell histamine content ($P < 0.05$ compared with spontaneous release). It is noteworthy that the

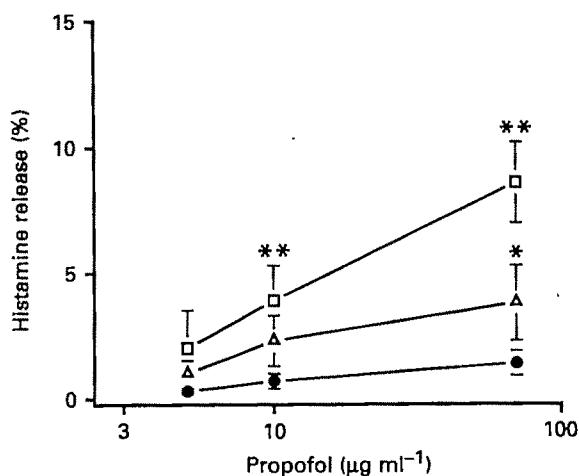


FIG. 1. Effect of various concentrations of propofol on histamine release from human basophils (●), lung parenchymal mast cells (HLMC) (□) and skin mast cells (HSMC) (△) (mean (SEM) obtained in 11 (basophils) and nine (HLMC and HSMC) experiments). * $P < 0.05$; ** $P < 0.01$ compared with spontaneous release.

TABLE I. Effect of various concentrations of propofol ($10\text{--}70\text{ }\mu\text{g ml}^{-1}$) on histamine release (ng/g wet weight of tissue) from human heart mast cells (mean of duplicate samples). — = Measurement not made

Experiment No.	Buffer	Histamine released (ng g^{-1})		
		Propofol ($\mu\text{g ml}^{-1}$)		
		10	35	70
1	74.0	75.0	—	43.0
2	33.5	36.7	—	37.2
3	41.0	35.0	—	59.0
4	24.0	30.0	—	46.0
5	55.0	50.0	28.0	30.0
6	26.0	—	29.0	17.0
7	26.0	14.0	26.0	33.0
Mean (SEM)	39.8 (7.0)	40.1 (8.4)	27.6 (0.8)	37.8 (5.0)

histamine-releasing activity of propofol from lung and skin mast cells varied markedly among different donors. In seven experiments, increasing concentrations of propofol failed to induce the release of histamine from mast cells present in human heart (table I).

In a second series of experiments, we compared the effects of increasing concentrations ($10^{-6}\text{--}10^{-3}\text{ mol litre}^{-1}$) of ketamine, including those reached *in vivo* [32], on histamine release from basophils and lung or skin mast cells.

TABLE II. Effect of ketamine, anti-IgE and A23187 on the de novo synthesis of LTC_4 or PGD_2 from human basophils and lung (HLMC) and skin mast cells (HSMC). *Concentrations used: $0.3\text{ }\mu\text{g ml}^{-1}$ in basophils, $1\text{ }\mu\text{g ml}^{-1}$ in HLMC, $3\text{ }\mu\text{g ml}^{-1}$ in HSMC. †Concentrations used: $0.2\text{ }\mu\text{g ml}^{-1}$ in basophils, $1\text{ }\mu\text{g ml}^{-1}$ in HLMC and HSMC. — = Not detectable

	LTC_4 ($\text{ng}/10^6$ basophils)	LTC_4 ($\text{ng}/10^6$ HLMC)	PGD_2 ($\text{ng}/10^6$ HSMC)
Experiment 1			
Ketamine (mol litre^{-1})			
3×10^{-4}	—	—	—
10^{-3}	—	—	—
Anti-IgE*	38.0	158.8	69.2
A23187†	290.4	468.3	228.4
Experiment 2			
Ketamine (mol litre^{-1})			
3×10^{-4}	—	—	—
10^{-3}	—	—	—
Anti-IgE*	43.8	204.0	115.1
A23187†	244.9	341.0	589.0

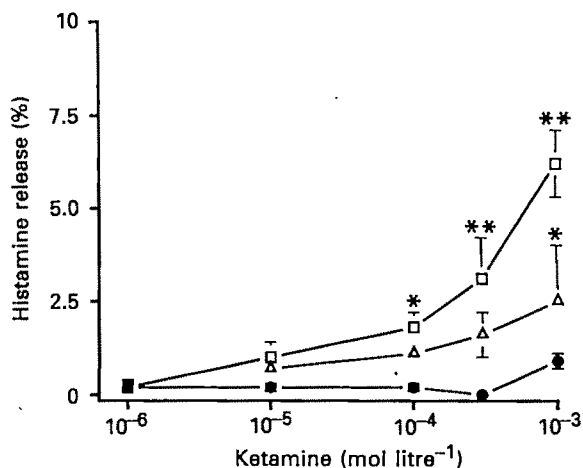


FIG. 2. Effect of various concentrations of ketamine on histamine release from human basophils (●), lung parenchymal mast cells (HLMC) (□) and skin mast cells (HSMC) (Δ) (mean (SEM) obtained in 14 (basophils), 12 (HLMC) and nine (HSMC) experiments). * $P < 0.05$; ** $P < 0.01$ compared with spontaneous release.

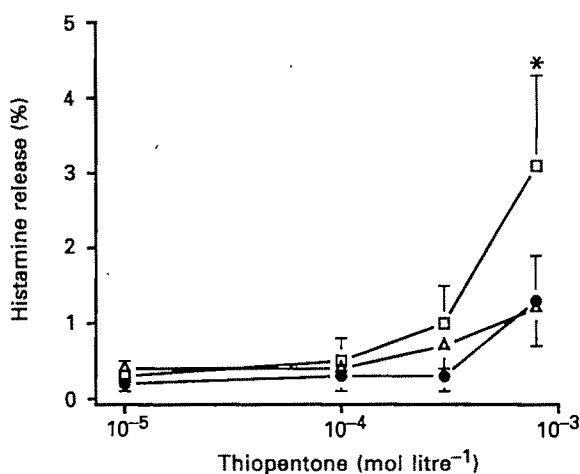


FIG. 3. Effect of various concentrations of thiopentone on histamine release from human basophils (●), lung parenchymal mast cells (HLMC) (□) and skin mast cells (HSMC) (Δ) (mean (SEM) obtained in eight (basophils), 10 (HLMC) and seven (HSMC) experiments). * $P < 0.05$ compared with spontaneous release.

Ketamine did not induce release of histamine from basophils obtained from 14 different donors (fig. 2). In contrast, ketamine induced histamine release from lung mast cells in a concentration-dependent manner ($P < 0.001$). In 12 experiments, ketamine released a maximum of 6.2 (0.9)% of lung mast cell histamine content ($P <$

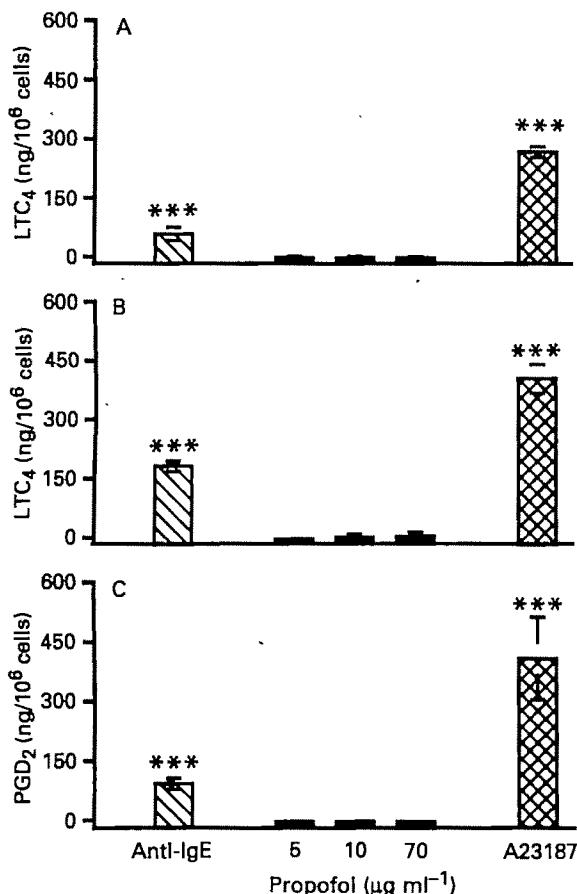


FIG. 4. Effect of anti-IgE ($0.3 \mu\text{g ml}^{-1}$ in basophils, $1 \mu\text{g ml}^{-1}$ in human lung mast cells (HLMC) and $3 \mu\text{g ml}^{-1}$ in human skin mast cells (HSMC)), propofol and A23187 ($0.2 \mu\text{g ml}^{-1}$ in basophils and $1 \mu\text{g ml}^{-1}$ in HLMC and HSMC) on the release of LTC₄ from human basophils (A) and lung mast cells (B), and of PGD₂ from skin mast cells (C) (mean (SEM) obtained in three experiments). *** $P < 0.001$ compared with spontaneous release.

0.01 compared with spontaneous release). The releasing activity of ketamine was variable and the per cent histamine release caused by ketamine $10^{-3} \text{ mol litre}^{-1}$ varied between 0% and 12% . The releasing activity of ketamine on skin mast cells was less marked ($P < 0.05$), and only the greatest concentration of ketamine caused a significant histamine release ($2.5 (1.5)\%$) ($P < 0.05$ compared with spontaneous release).

We next investigated the effects of various concentrations (10^{-6} – $8 \times 10^{-4} \text{ mol litre}^{-1}$) of thiopentone, including those reached *in vivo* [32], on histamine release from basophils and mast cells. These concentrations of thiopentone failed to

induce histamine release from both basophils and skin mast cells (fig. 3). Only the greatest concentration ($8 \times 10^{-4} \text{ mol litre}^{-1}$) of thiopentone caused significant release from lung mast cells ($3.1 (1.2)\%$) ($P < 0.01$ compared with spontaneous release).

The activation of human basophils and lung but not skin mast cells leads to the *de novo* synthesis of LTC₄ through the 5-lipoxygenase pathway [24, 25] in addition to the secretion of preformed histamine. Both lung and skin mast cells, but not basophils, also synthesize PGD₂ through the cyclo-oxygenase pathway [19, 24]. We investigated the effects of various concentrations of propofol, ketamine and thiopentone on the *de novo* synthesis of mediators from basophils and mast cells. Ketamine failed to induce the synthesis of LTC₄ from basophils and lung mast cells and of PGD₂ from skin mast cells (table II). As a control, anti-IgE and the Ca²⁺ ionophore A23187 stimulated the synthesis of LTC₄ or PGD₂. Similar results were obtained with thiopentone. Similarly, propofol did not induce the *de novo* synthesis of LTC₄ from basophils and lung mast cells or PGD₂ from skin mast cells (fig. 4). In the same experiments, anti-IgE and A23187 caused the *de novo* synthesis of these mediators.

DISCUSSION

Our results indicate that general anaesthetics induce histamine release selectively from mast cells and that mast cells isolated from different anatomical sites (lung parenchyma, skin tissue and heart fragments) can be useful to evaluate *in vitro* the histamine releasing capacity of general anaesthetics.

Previous studies have demonstrated that skin mast cells are exquisitely sensitive to atracurium, tubocurarine [33] and morphine [23, 34]. Our results extend these observation by demonstrating the existence of different types of heterogeneity. First, histamine-containing cells (basophil granulocytes and mast cells isolated from different anatomical sites) showed a remarkable degree of heterogeneity in response to the same type of general anaesthetic. In fact, we have demonstrated that peripheral blood basophils are essentially unresponsive to the wide spectrum of concentrations of general anaesthetics used in this study. Therefore, the *in vitro* model of basophil histamine release, which is potentially useful to detect patients who possess specific IgE against an

epitope present in neuromuscular blocking drugs [35], does not lend itself to the study of anaphylactoid reactions. There is also a remarkable degree of heterogeneity among mast cells obtained from different human tissues. For example, pharmacological concentrations of propofol induced histamine release from lung mast cells, whereas they had a more modest or no effect on skin and heart mast cells, respectively. Finally, we found that the general anaesthetics used in this study possess a remarkable degree of heterogeneity in their releasing capacity among different donors. The latter observation might be clinically relevant because it is well known that anaphylactoid reactions occur only in a small proportion of patients undergoing general anaesthesia. Therefore, the heterogeneity of the response of human $Fc\epsilon RI^+$ cells—that is, the histamine-releasing capacity shown by different general anaesthetics and the degree of the response of mast cells obtained from different donors—might explain, at least in part, the wide spectrum of the anaphylactoid reactions observed in different patients after administration of these drugs.

In the present study, thiopentone induced a small amount of histamine release from skin mast cells. This is in apparent contrast to the findings reported by Hirshman and colleagues [12]. However, they used greater concentrations of thiopentone and their system to challenge skin mast cells differed from ours: they used fragments of infants foreskin, while we used mast cells enzymatically dispersed from skin obtained from adults, and there is evidence that the age of cell donors influences the release of human basophils [36] and of mast cells [19, 22].

Propofol [16, 17], ketamine [9] and thiopentone [7, 37] may induce haemodynamic alterations in man, caused presumably by histamine release *in vivo* [6, 7]. Histamine administration reproduces most of the metabolic and haemodynamic effects observed during anaphylactic/anaphylactoid reactions [13–15]. However, other mediators synthesized by human basophils and mast cells (LTC_4 and PGD_2) might contribute to these effects [38]. We have demonstrated that the general anaesthetics used in this study did not induce the *de novo* synthesis of LTC_4 or PGD_2 from human basophils and mast cells. This novel observation might indicate that histamine H_1 - and H_2 -blockers could be sufficient to prevent the anaphylactoid reaction caused by these drugs, as shown previously for morphine [39, 40].

The *in vitro* concentrations that we used include those usually found in the peripheral blood of patients undergoing general anaesthesia [32]. Therefore, the local concentrations of these drugs during or immediately after i.v. infusion might be relevant, considering also the variability in the releasing activity of cells from different donors and the variations of pharmacokinetics in different clinical conditions [32].

In conclusion, our results are the first systematic evaluation of the histamine-releasing activity of three commonly used i.v. anaesthetic agents using three different *in vitro* systems. We have demonstrated that these agents induce only histamine release selectively from mast cells. These findings might, at least in part, explain one of the mechanisms of anaphylactoid reactions caused by these drugs in some patients undergoing general anaesthesia. The experimental models described here might be useful to extend the present knowledge of the property of several anaesthetics to release histamine from human basophils and mast cells.

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REFERENCES

1. Laxenaire MC, Moneret-Vautrin DA, Vervloet D, Alazia M, François G. Accidents anaphylactoides graves perianesthésiques. *Annales Françaises Anesthésie et Réanimation* 1985; 4: 30–46.
2. Clarke RSJ. Clinical features and changing trends in hypersensitivity reactions. *Annales Françaises Anesthésie et Réanimation* 1985; 4: 146–151.
3. Laxenaire MC, Moneret-Vautrin DA, Vervloet D. The French experience of anaphylactic reactions. In: Sage DJ, ed. *International Anesthesiology Clinics: Anaphylactoid Reactions in Anesthesia*. Boston: Little, Brown, 1985; 145–160.
4. Clarke RSJ. Hypersensitivity reactions to intravenous

- anaesthetic drugs. In: Atkinson RS, Hewer CL, eds. *Recent Advances in Anaesthesia and Analgesia*, Vol. 14. Edinburgh: Churchill-Livingstone, 1982; 55-79.
5. Clarke RSJ, Dundee JW, Garrett RT, McArdle GK, Sutton JA. Adverse reactions to intravenous anaesthetics. *British Journal of Anaesthesia* 1975; 47: 575-585.
 6. Lorenz W, Doenicke A, Schöning B, Neugebauer E. The role of histamine in adverse reactions to intravenous agents. In: Thornton G, ed. *Adverse Reactions of Anaesthetic Drugs*. New York, Amsterdam: Elsevier, 1981; 169-238.
 7. Lorenz W, Doenicke A, Meyer R, Reimann HJ, Kusche J, Barth H, Geesing H, Hutzl M, Weissenbaker B. Histamine release in man by propofol and thiopentone: pharmacological effects and clinical consequences. *British Journal of Anaesthesia* 1972; 44: 355-368.
 8. Wright PJ, Shortland JR, Stevens JD, Parsons MA, Watkins J. Fatal haemopathological consequences of general anaesthesia. *British Journal of Anaesthesia* 1989; 62: 104-107.
 9. Mathieu A, Goudsouzian N, Snider MT. Reaction to ketamine: anaphylactoid or anaphylactic? *British Journal of Anaesthesia* 1989; 62: 104-107.
 10. Watkins J, Thornton JA. Immunological and non-immunological mechanisms involved in adverse reactions to drugs. *Klinische Wochenschrift* 1982; 60: 958-964.
 11. Moss J, Rosow CE, Savarese JJ, Philbin DM, Kniffen KJ. Role of histamine in the hypotensive action of d-tubocurarine in humans. *Anesthesiology* 1981; 55: 19-25.
 12. Hirshman CA, Edelstein RA, Ebertz JM, Hanifin JM. Thiobarbiturate-induced histamine release in human skin mast cells. *Anesthesiology* 1985; 63: 353-356.
 13. Vigorito C, Russo P, Picotti GB, Chiariello M, Poto S, Marone G. Effects of histamine infusion in man. *Journal of Cardiovascular Pharmacology* 1983; 5: 531-537.
 14. Vigorito C, Poto S, Picotti GB, Triggiani M, Marone G. Effects of activation of the H_1 receptor on coronary hemodynamics in man. *Circulation* 1986; 73: 1175-1182.
 15. Vigorito C, Giordano A, De Caprio L, Vitale DF, Maurea N, Silvestri P, Tuocillo B, Ferrara N, Marone G, Rengo F. Effects of histamine on coronary hemodynamics in man: role of H_1 and H_2 receptors. *Journal of the American College of Cardiology* 1987; 10: 1207-1213.
 16. Briggs LP, Clarke RSJ, Watkins J. An adverse reaction to the administration of disoprofol "Diprivan". *Anaesthesia* 1982; 37: 1099-1101.
 17. Doenicke A, Lorenz W, Stanworth D, Duka T, Glen GB. Effects of propofol ("Diprivan") on histamine release, immunoglobulin levels and activation of complement in healthy volunteers. *Postgraduate Medical Journal* 1985; 61 (Suppl. 3): 15-20.
 18. Casolaro V, Galeone D, Giacummo A, Sanduzzi A, Melillo G, Marone G. Human basophil/mast cell releasability. V. Functional comparisons of cells obtained from peripheral blood, lung parenchyma and from bronchoalveolar lavage in asthmatics. *American Review of Respiratory Disease* 1989; 139: 1375-1382.
 19. Lawrence ID, Warner JA, Cohan VL, Hubbard WC, Kagey-Sobotka A, Lichtenstein LM. Purification and characterization of human skin mast cells. Evidence for human mast cell heterogeneity. *Journal of Immunology* 1987; 139: 3062-3069.
 20. Marone G, Triggiani M, Cirillo R, Giacummo A, Hammarström S, Condorelli M. IgE-mediated activation of human heart *in vitro*. *Agents and Actions* 1986; 18: 194-196.
 21. Marone G, Casolaro V, Cirillo R, Stellato C, Genovese A. Pathophysiology of human basophils and mast cells in allergic disorders. *Clinical Immunology and Immunopathology* 1989; 50: S24-S40.
 22. Lowman MA, Rees PH, Benyon RC, Church MK. Human mast cell heterogeneity: histamine release from mast cells dispersed from skin, lung, adenoids, tonsils, and colon in response to IgE-dependent and nonimmunologic stimuli. *Journal of Allergy and Clinical Immunology* 1988; 81: 590-597.
 23. Tharp MD, Kagey-Sobotka A, Fox CC, Marone G, Lichtenstein LM, Sullivan TJ. Functional heterogeneity of human mast cells from different anatomic sites: *in vitro* responses to morphine sulphate. *Journal of Allergy and Clinical Immunology* 1987; 79: 646-653.
 24. Patella V, Casolaro V, Björck L, Marone G. Protein L: an Ig-binding protein that activates human basophils and mast cells. *Journal of Immunology* 1990; 145: 3054-3061.
 25. Marone G, Casolaro V, Paganelli R, Quinti I. IgG anti-IgE from atopic dermatitis induces mediator release from basophils and mast cells. *Journal of Investigative Dermatology* 1989; 93: 246-252.
 26. Siraganian RP. An automated continuous-flow system for the extraction and fluorimetric analysis of histamine. *Analytical Biochemistry* 1974; 57: 383-394.
 27. Marone G, Cirillo R, Genovese A, Marino O, Quattrin S. Human basophil/mast cell releasability. VII. Heterogeneity of the effect of adenosine on mediator secretion. *Life Sciences* 1989; 45: 1745-1754.
 28. Gilbert HS, Ornstein L. Basophil counting with a new staining method using Alcian blue. *Blood* 1975; 46: 279-286.
 29. Marone G, Columbo M, Triggiani M, Cirillo R, Genovese A, Formisano S. Inhibition of IgE-mediated histamine and peptide leukotriene release from human basophils and mast cells by forskolin. *Biochemical Pharmacology* 1987; 36: 13-20.
 30. Hayes EC, Lombardo DL, Girard JY, Maycock AL, Rokach J, Rosenthal AS, Young RN, Egan RW, Zweerink HJ. Measuring leukotrienes of slow reacting substance of anaphylaxis: development of a specific radioimmunoassay. *Journal of Immunology* 1983; 131: 429-436.
 31. Scheffer WC. *Statistics for Health Professionals*. Reading, MA: Addison-Wesley Publishing Company, 1984.
 32. Prys-Roberts C, Hug CC jr. *Pharmacokinetics of Anaesthesia*. Oxford: Blackwell Scientific Publications, 1984.
 33. North FC, Kettelkamp N, Hirshman CA. Comparison of cutaneous and *in vitro* histamine release by muscle relaxants. *Anesthesiology* 1987; 66: 543-546.
 34. Fewtrell CMS, Foreman JC, Jordan CC, Oehme P, Renner H, Stewart JM. The effects of substance P on histamine and 5-hydroxytryptamine release in rat. *Journal of Physiology (London)* 1982; 330: 393-411.
 35. Vervloet D, Arnaud A, Senft M, Dor P, Bongrand P, Charpin C, Alazia M. Leukocyte histamine release to suxamethonium in patients with adverse reactions to muscle relaxants. *Journal of Allergy and Clinical Immunology* 1985; 75: 338-342.
 36. Marone G, Poto S, di Martino L, Condorelli M. Human basophil releasability. I. Age-related changes in basophil releasability. *Journal of Allergy and Clinical Immunology* 1986; 77: 377-383.

37. Hirshman CA, Peters J, Cartwright-Lee I. Leukocyte histamine release to thiopentone. *Anesthesiology* 1982; 56: 64-67.
38. Marone G, Giordano A, Cirillo R, Triggiani M, Vigorito C. Cardiovascular and metabolic effects of peptide leukotrienes in man. *Annals of the New York Academy of Sciences* 1988; 524: 321-333.
39. Philbin DM, Moss J, Akins CW, Rosow CE, Kono K, Schneider RC, VerLee TR, Savarese JJ. The use of H_1 and H_2 antagonists with morphine anesthesia: a double-blind study. *Anesthesiology* 1981; 55: 292-296.
40. Tryba M, Zevounou F, Zenz M. Prevention of histamine-induced reactions during the induction of anaesthesia following premedication with H_1 - + H_2 -antagonists i.m. *British Journal of Anaesthesia* 1986; 58: 478-482.

FIRST PASS LUNG UPTAKE OF BUPIVACAINE: EFFECT OF ACIDOSIS IN AN INTACT RABBIT LUNG MODEL

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SUMMARY

The first pass uptake, metabolism and recovery of bupivacaine were examined in an intact rabbit lung model using a multiple indicator technique with rapid sequential sampling. The rabbits were allocated to an acidotic group (pH 7.0-7.1) (n = 8) and a control group (n = 10) with normal pH. Bupivacaine recovery rates were not significantly different: median 93.2% (range 48.9-116.5%) and 94.5% (54.9-123.1%) in control and acidotic groups, respectively. Median peak percentage fractional concentrations of bupivacaine were greater in the acidotic group: 6.22% (2.5-7.65%) vs 4.1% (2.5-6.7%) (P < 0.05). Median maximum instantaneous pulmonary percentage extraction was less in the acidotic animals than in animals with normal pH: 81.2% (47.1-91.9%) vs 91.0% (82.6-94.5%) (P < 0.01). Median normalized mean percentage transit time was less in the acidotic group (245.3% (163.4-465.3%)) than in the control group (423.9% (313.9-740.4%)) (P < 0.01). There was no evidence for bupivacaine metabolism by the lung. The results suggest that acidosis reduced bupivacaine lung uptake and increased its rate of passage through the lung, but did not influence overall drug recovery rates. This has clinical implications for bupivacaine related cardiac and cerebral toxicity.

KEY WORDS

Anaesthetics, local: bupivacaine. Biotransformation: acidosis, lung.

Bupivacaine is an amide local anaesthetic agent which has been associated particularly with cardiotoxicity [1-4] which may occur after either inadvertent i.v. injection or sudden release of a tourniquet during i.v. regional anaesthesia. Blood concentrations of bupivacaine reaching the sys-

temic circulation are buffered by the first pass effect of the lung [5]. Acidosis, which increases the ionized bupivacaine fraction, may reduce pulmonary uptake and therefore increase the potential for CNS and cardiac toxicity. The present studies were undertaken to examine the influence of acidaemia on the uptake of bupivacaine by an intact rabbit lung preparation.

In this communication the following terms are used to define drug fluxes: *uptake* or *extraction* describes the quantity of drug passing into lung tissue. Uptake may be followed by *accumulation* and *metabolism*; simultaneously there may be *back diffusion* of drug from lung tissue or pulmonary vascular endothelial sites to pulmonary circulation. The nett loss of drug after a single passage through the lungs (the result of uptake, accumulation, metabolism and back diffusion) is defined as drug *removal*. The percentage of drug *recovered* is the difference between drug *removal* and 100%.

MATERIALS AND METHODS

The first pass uptake and metabolism of bupivacaine by the lung was examined using a multiple indicator bolus technique in an intact rabbit lung model. Eighteen New Zealand White rabbits (weights 2-3.5 kg), fed freely on a diet of R.P.G. (E. Dixons and Sons (Ware) Ltd, Herts) were anaesthetized with 4% halothane in oxygen. The trachea was intubated with a 3.5-mm Portex tracheal tube (via a tracheostomy) and the lungs ventilated with 1% halothane in oxygen. Blood-gas tensions were measured at 20-min intervals

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and ventilation adjusted to maintain normocapnia. Temperature was maintained by placing the animals on a thermostatically controlled warming blanket and monitored with a rectal probe (Digitec 5800 thermometer probe, United Systems Corp., Dayton, Ohio). A 16-gauge Abbocath cannula (Abbot Ireland Ltd) was placed in the left jugular vein and maintenance fluids infused as normal saline $5 \text{ ml kg}^{-1} \text{ h}^{-1}$. The right jugular vein was cannulated with a 5-French gauge Berman angiographic balloon catheter (Critikon Inc., Tampa, U.S.A.) and passed into the right ventricle. Both carotid arteries were cannulated with 16-gauge catheters which were joined by a Y-piece, thus converging carotid flow. Airway pressure, carotid artery and right ventricular pressures were monitored (Gould T150AD transducers, Bilthoven, Netherlands) and recorded continuously on a Lectromed M19 6 channel recorder. End-tidal carbon dioxide concentration (Gould Capnograph Mk III) and ECG were recorded. Animal preparation time was 45–60 min.

The rabbits were allocated to two groups. Ten animals were treated as controls and the pH was kept in the normal range (pH 7.35–7.45). The other eight animals were made acidotic (pH 7.0–7.1) by i.v. infusion of hydrochloric acid $0.15 \text{ mol litre}^{-1}$ into the left jugular vein. After the animals had been at the appropriate pH for 10 min, 20 ml of blood was taken for calibration of the injectate. The injectate (0.4 ml) contained: 0.75% bupivacaine 0.1 ml (0.75 mg), 0.25% indocyanine green (ICG) 0.2 ml (0.5 mg), sterile water 0.1 ml, and ^3H -bupivacaine $10 \mu\text{l}$ (labelled on the methyl groups of the xylylidine moiety of molecule).

Each rabbit received a 0.4-ml bolus of injectate into the right ventricular catheter, followed immediately by normal saline 2 ml injected over 2 s. Nine, 3-s samples were collected manually by a second operator from the continuous carotid artery catheter flow. The first sample was collected from time 0 (bolus given) for 3 s and designated the "zero" sample. The total volume of blood collected during sampling varied between 18 and 28 ml depending on flow rate through the carotid catheters. It was assumed that there was full mixing of the injectate with blood after passage through the right ventricle, lungs and left heart. Each blood sample (including the calibration samples) were divided so that three separate estimations could be made. Whole blood 0.1 ml was placed in a glass scintillation tube and prepared for hydrogen-3 beta counting; the

remainder of the sample was spun at 3500 g and the supernatant plasma used for measurement of bupivacaine by gas-liquid chromatography (GLC) [6] and ICG by spectrophotometry at 805 nm (PU 8600 series UV/VIS, Pye Unicam, Cambridge, U.K.). GLC measurements of bupivacaine had a sensitivity of $0.01 \text{ mg litre}^{-1}$, a within-batch coefficient of variation of 7.1% at 1 mg litre^{-1} and 1.4% at $12.5 \text{ mg litre}^{-1}$; between-batch coefficient of variation was 3.9%. ICG measurements had a coefficient of variation of 15% at 0 mg litre^{-1} , 1.5% at 10 mg litre^{-1} and 0.8% at 20 mg litre^{-1} . ICG, bupivacaine and hydrogen-3 concentrations were expressed as percentage fractional concentrations of the injectate. It was assumed that ICG remained in the vascular compartment and that this was unaffected by acidosis.

Calculations for the pharmacokinetic parameters were as follows: maximum instantaneous bupivacaine extraction was calculated as $100 ((\text{concn ICG} - \text{concn Bup}) / \text{concn ICG})$ where concn denotes the fractional concentration of the injectate.

The area under the curve (AUC) of the fractional concentration of injectate was calculated from time zero to infinity. The first moment (AUMC) was calculated as the area under the curve (from zero to infinity) for AUC against time.

Percentage recovery of bupivacaine was determined from $100 (\text{AUC bupivacaine} / \text{AUC ICG})$, whereas percentage bupivacaine removal was calculated as $(\text{AUC ICG} - \text{bupivacaine recovery})$, where AUC ICG was assumed to be 100.

The mean transit times (MTT) for ICG and bupivacaine were derived from the ratio of the first and zero moments, $\text{AUMC} : \text{AUC (s)}$. The MTT for bupivacaine was expressed relative to that of ICG—normalized bupivacaine MTT (%) = $100 (\text{MTT bupivacaine} / \text{MTT ICG})$.

The volume of distribution (ml) was calculated from $\text{MTT (s)} \times \dot{Q} / 60$, where $\dot{Q}$ is the cardiac output (ml min^{-1}) calculated from the ICG curve.

The pulmonary extravascular volume of distribution occupied by bupivacaine was calculated as the volume of distribution for bupivacaine volume minus ICG volume of distribution.

Data were compared by Student's unpaired *t* tests and Mann-Whitney *U* test as appropriate. Statistical significance was assumed if $P < 0.05$. Data are shown as median (range) unless indicated otherwise.

RESULTS

Cardiac output in the two groups was determined from the ICG dye dilution curve of the multiple indicator bolus. There was no difference in mean cardiac output between the two groups (table I).

The mean percentage fractional concentrations of ICG and ^3H -bupivacaine were plotted against time (fig. 1); peak concentrations of bupivacaine were both less and delayed compared with ICG.

Recovery of ^3H -bupivacaine was determined by expressing the ^3H -bupivacaine AUC as a percentage of AUC ICG. The area under the curves for ^3H -bupivacaine and ICG included AUC up to

TABLE I. Cardiac output (CO) for each animal, and mean (SEM) for the group

Rabbit No.	CO (ml min ⁻¹)	
	Control	Acidotic
1	206.8	235.2
2	247.3	350.0
3	300.2	408.5
4	347.2	338.0
5	204.6	252.7
6	238.4	247.9
7	615.4	551.3
8	316.4	143.7
9	259.9	
10	314.2	
Mean	305.0	315.9
SEM	37.7	44.3

the point of recirculation, plus the AUC of the concentration-time curves extended to infinity, calculated assuming a mono-exponential decay from a point before recirculation. Median recovery of ^3H -bupivacaine after first pass was similar in both groups (table II). Median peak percentage fractional concentrations of bupivacaine (at 6 s) were greater in the acidotic animals (6.2% (2.5–7.6%)) than the controls (4.1% (2.5–6.7%)) ($P < 0.05$). The median maximum instantaneous percentage extractions (uptake) were less in the acidotic group (81.2% (47.1–91.9%)) than in the normal animals (91.0% (82.6–94.5%)) ($P < 0.01$) (fig. 1).

The recovery of ^3H -bupivacaine may have included ^3H -labelled bupivacaine metabolites. In order to distinguish bupivacaine from its metabolites, bupivacaine was measured also by GLC. A difference in AUC between GLC and hydrogen-3 estimations of bupivacaine would suggest that some of the label originates from bupivacaine metabolites. Table II shows the ratios of GLC to ^3H -AUC expressed as a percentage. The median percentages were 100.5 and 101.9 for the control and acidotic rabbits, respectively, suggesting that the measurements of bupivacaine were sufficiently similar to exclude significant metabolism during passage through the lung.

MTT for the passage of ICG and ^3H -bupivacaine was calculated from the ratio AUMC: AUC, where AUMC is the first moment of the curve [7–9]. MTT was significantly greater for

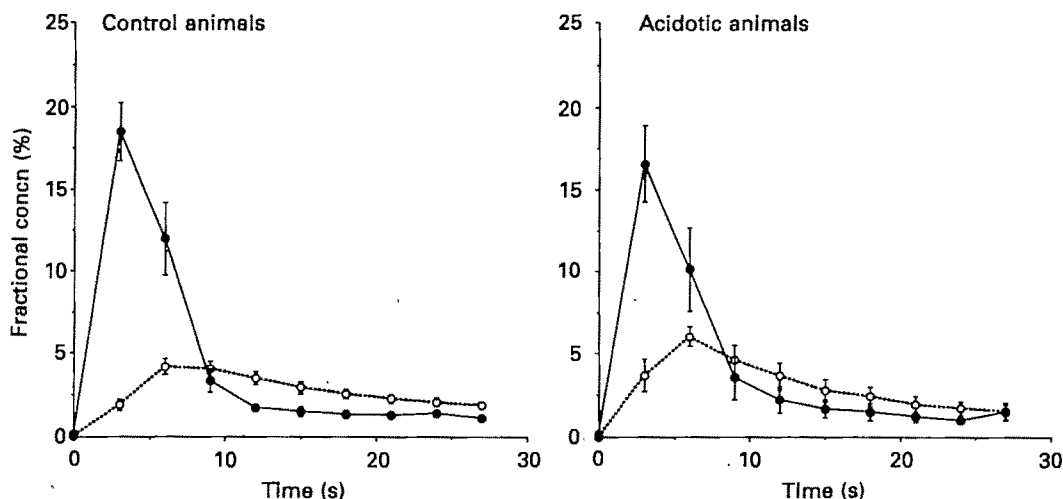


FIG. 1. Changes (mean, SEM) in percentage fractional concentrations of bupivacaine (○) and indocyanine green (●) in the carotid artery with time after a multiple indicator bolus into the right ventricle of control animals with normal pH (left) and acidotic animals (pH 7.0–7.1) (right).

TABLE II. Kinetics of ^3H -bupivacaine for each rabbit, and median values. GLC = Gas-liquid chromatography; β = beta counting; MTT = mean transit time; Pulm. extravasc. VD = pulmonary extravascular volume of distribution. See text for details. * $P < 0.05$ compared with control

	Recovery (%)		AUC GLC:AUC β (%)		Normalized MTT (%)		Pulm. extravasc. VD (ml)	
	Control	Acidotic	Control	Acidotic	Control	Acidotic	Control	Acidotic
1	87.6	94.2		93.4	347.3	406.0	46.8	59.9
2	95.6	84.6	95.0	129.9	461.2	465.3	72.9	54.2
3	48.9	100.5	146.2	93.0	740.4	189.7	166.6	23.8
4	74.7	78.8	109.2	114.4	491.6	163.4	108.8	18.6
5	106.4	94.8	68.2	91.1	386.7	216.9	66.4	32.0
6	90.3	102.4	79.5	103.5	313.9	316.6	36.5	48.3
7	92.4	54.9	78.2	145.0	354.3	224.4	120.0	46.8
8	103.5	123.1	106.0	100.3	330.3	266.3	68.0	37.8
9	94.0				595.6		98.7	
10	116.5		135.6		717.0		151.8	
Median	93.2	94.5	100.5	101.9	423.9	245.3*	85.8	42.3*

^3H -bupivacaine than ICG in both groups ($P < 0.01$). When MTT for the passage of ^3H -bupivacaine through the lung was normalized for the cardiac output (ratio of MTT ^3H -bupivacaine to MTT ICG expressed as a percentage (table II)), the median normalized MTT % in the acidotic animals was found to be shorter than in the control group ($P < 0.01$).

The pulmonary extravascular volume of distribution for bupivacaine (calculated by subtracting the ICG volume of distribution from the ^3H -bupivacaine volume of distribution) was significantly greater in control animals than in the acidotic animals ($P < 0.05$) (table II).

DISCUSSION

The ability of the lung to take up local anaesthetics has been described by several authors. In 1966 Åkerman demonstrated that lignocaine and prilocaine were concentrated in the lungs of rats after i.p., i.m. or s.c. injections [10]. Tucker and Boas showed that the lung was able to buffer high systemic concentrations of lignocaine when the drug was given as an i.v. bolus [11]. There have been many reports of difficulties in the resuscitation of patients and experimental animals after cardiac arrest caused by bupivacaine [1-4]. As local anaesthetics in high doses may cause cerebral and cardiac toxicity, the potential buffering ability of the lung and factors that may influence it are of interest to the anaesthetist.

Studies on the lung uptake of bupivacaine are contradictory. Sjöstrand and Widman noted that

concentrations of radiolabelled bupivacaine in anaesthetized rabbit lung were eight times greater than in blood [12]. Irestedt, Andreen and Belfrage examined bupivacaine uptake by the dog lung by measuring concentration differences between the pulmonary and femoral artery for 60 min after i.m. injection [13]. During the first 10 min, nine of their 10 dogs showed arterio-venous differences in bupivacaine concentration across the lungs, suggesting pulmonary uptake. However, when these concentration differences were measured at 20, 30 and 60 min, they were so small that the authors concluded that the lung played little role in bupivacaine disposition. Rothstein, Cole and Pitt examined the relationship between dose of bupivacaine and bupivacaine extraction (uptake) with a multiple indicator technique in a rabbit model [5]. They showed that maximum instantaneous bupivacaine uptake varied between 73 and 85% and decreased as the dose increased. Previous work in an *in situ* isolated perfused rabbit lung model has shown that an initial large uptake is followed later by back diffusion of bupivacaine into the pulmonary circulation [14].

In the current study an intact model was used with a multiple indicator technique. One group of animals was made acidotic whereas the other group was maintained at a normal pH. Acidosis considerably shortened the mean transit time, increased peak bupivacaine concentrations and decreased the maximum instantaneous extraction fraction. However, acidosis did not alter the overall recovery rate for bupivacaine. Acidosis also reduced the extravascular pulmonary volume

of distribution of bupivacaine. The maximum instantaneous extraction of bupivacaine in this study compares well with previous work [5].

Local anaesthetic agents are secondary or tertiary basic amines with pK_a values between 7.7 and 9.5. A small change in pH for an agent with a pK_a near the physiological range would be expected to have a significant effect on the ionized:unionized ratio. The ionized form (cationic) is water soluble, whereas the base is lipid soluble [15]. Acidosis promotes the production of the cation and therefore would be predicted to reduce pulmonary uptake of drug. Bupivacaine is a tertiary basic amine with a pK_a of 8.2. At physiological pH it is predominantly in the unionized form (84.6%); at pH 7.0 this increases to 93.7%.

Sjöstrand and Widman [12] showed that, under conditions of metabolic acidosis (pH 7.24), the lung:blood concentration ratio was 19.5, compared with 8 under normal conditions. They suggested that this increase in lung affinity for bupivacaine in acidosis was the result of increased tissue binding by the water soluble form of bupivacaine. However, Post and his colleagues showed that acidotic rat lung slices had decreased uptake of bupivacaine [16].

The present study supports the finding that acidosis decreases the pulmonary uptake of bupivacaine, resulting in greater peak concentrations and a faster passage through the pulmonary circulation. It is noteworthy that there was no difference in bupivacaine recovery between the acidotic and control animals when the curves were extended to infinity. It would therefore seem that, in spite of differences in initial lung uptake of bupivacaine, bupivacaine eventually diffuses back into the circulation. Our study found no evidence for metabolism of bupivacaine by the lung. A possible implication of these findings is that systemic or localized acidosis, such as may be found in an ischaemic limb during a Bier's block, may be more likely to promote cerebral and cardiac toxicity after inadvertent entry of bupivacaine into the circulation.

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REFERENCES

1. Albright G. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; 51: 285-286.
2. Prentiss J. Cardiac arrest following caudal anesthesia. *Anesthesiology* 1979; 50: 51-53.
3. Marx G. Cardiotoxicity of local anesthetics—the plot thickens. *Anesthesiology* 1984; 60: 3-5.
4. Rosenberg P, Kalso E, Tuominen M, Linden H. Acute bupivacaine toxicity as a result of venous leakage under the tourniquet cuff during a Bier block. *Anesthesiology* 1983; 58: 95-98.
5. Rothstein P, Cole J, Pitt B. Pulmonary extraction of ^3H -bupivacaine; modification by dose, propranolol and interaction with ^{14}C 5-hydroxytryptamine. *Journal of Pharmacology and Experimental Therapeutics* 1987; 240: 410-414.
6. Mather L, Tucker G. Meperidine and other basic drugs: general method for their determination in plasma. *Journal of Pharmaceutical Sciences* 1974; 63: 206-207.
7. Meier P, Zierler KL. On the theory of the indicator dilution method for measurement of blood flow and volume. *Journal of Applied Physiology* 1954; 6: 731-744.
8. Zierler K. Theoretical basis of indicator dilution methods for measuring flow and volume. *Circulation Research* 1962; 10: 393-407.
9. Riegelman S, Collier P. The application of statistical moment theory to the evaluation of *in vivo* dissolution time and absorption time. *Journal of Pharmacokinetics and Biopharmaceutics* 1980; 8: 509-534.
10. Åkerman B, Åström A, Ross S, Telc A. Studies on the absorption, distribution and metabolism of labelled prilocaine and lidocaine in some animal species. *Acta Pharmacologica et Toxicologica* 1966; 24: 389-403.
11. Tucker GT, Boas R. Pharmacokinetic aspects of intravenous regional anesthesia. *Anesthesiology* 1971; 34: 538-549.
12. Sjöstrand U, Widman B. Distribution of bupivacaine in the rabbit under normal and acidotic conditions. *Acta Anaesthesiologica Scandinavica* 1973; (Suppl.) 50: 5-24.
13. Irestedt L, Andreen M, Belfrage P. Uptake of bupivacaine (Marcaine) in liver and lung after intramuscular administration in the dog. *Acta Anaesthesiologica Scandinavica* 1976; 20: 361-368.
14. Palazzo M. The lung as a first pass organ (M.D. Thesis). Bristol: Bristol University, 1988.
15. de Jong R. Clinical physiology of local anesthetic action. In: Cousins M, Bridenbaugh P, eds. *Neural Blockade*. Philadelphia: J. B. Lippincott, 1980: 21-44.
16. Post C, Andersson RG, Ryrfeldt A, Nilsson E. Physicochemical modification of lidocaine uptake in rat lung tissue. *Acta Pharmacologica et Toxicologica* 1979; 44: 103-109.

PATHOGENESIS OF SUXAMETHONIUM-INDUCED MUSCLE DAMAGE IN THE BIVENTER CERVICIS MUSCLE IN THE CHICK

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SUMMARY

Muscle damage induced by suxamethonium, and the influence of halothane on it, has been examined by measuring the efflux of creatine kinase (CK) in the biventer cervicis muscle of the chick. Whereas halothane and suxamethonium alone did not increase the enzyme efflux significantly, the combination of the two was associated with significant increase in the concentration of CK in the bathing medium by 59-157%. The increase in CK was prevented by adding chlorpromazine 100 $\mu\text{mol litre}^{-1}$ to the medium, suggesting the involvement of phospholipases in the pathogenesis of suxamethonium-induced muscle damage.

KEY WORDS

Anaesthetics, volatile: halothane. Complications: muscle damage, creatine kinase efflux. Neuromuscular relaxants: suxamethonium.

Suxamethonium has several side effects, the most common of which are muscular in origin. The association between administration of suxamethonium and delayed muscle pains has been long recognized [1]. It is also known to cause an increase in serum concentrations of creatine kinase (CK), which has been regarded as an index of muscle damage in both *in vivo* and *in vitro* studies [2-4].

Little is known about the aetiology of suxamethonium-induced muscle damage. Several theories have been proposed, but the acute nature of the condition has made it difficult to define its pathogenesis. It has been suggested that endplate depolarization by suxamethonium produces an influx of calcium ions into the myoplasm, causing activation of phospholipases and culminating in cellular damage [5]. In addition, there is evidence

that similar calcium-mediated processes are responsible for muscle damage in other situations [6-8]. In the present study, we have examined the effect of suxamethonium on the efflux of CK from the biventer cervicis muscle of the young chick. This muscle contains a large proportion of multiply-innervated fibres, with cholinergic receptors distributed all over the sarcolemma, thus rendering it markedly sensitive to suxamethonium-induced membrane depolarization [9].

MATERIALS AND METHODS

The study was carried out in two phases. In the first phase, we examined the release of CK in response to suxamethonium and the effect of halothane on this. In the second phase, the influence of chlorpromazine, which inhibits phospholipase A2 [10], was assessed on limitation of muscle damage as measured by the same enzyme efflux.

Phase 1. One-day old chicks weighing 45-50 g were killed in an ether chamber and the biventer cervicis muscle dissected out as described by Ginsborg and Warriner [9]. This muscle lies in the dorsum of the neck, arises from the base of the skull and is inserted into the supraspinous ligament. It has two bellies, separated by a tendon. The lower muscle belly was removed, mounted on holders and suspended in tubes containing 6 ml of freshly prepared bicarbonate-buffered Krebs

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solution modified to produce free calcium concentration of $1 \text{ mmol litre}^{-1}$ (constituents (mmol litre^{-1}): NaCl 120, KCl 5.9, NaHCO_3 23, $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ 1.2, glucose 5.5, MgCl_2 1.2, and CaCl_2 1.0). The medium was gassed with 5% carbon dioxide in oxygen and maintained in a thermostatically controlled water bath at 37°C .

After isolation, each muscle was incubated for 30 min to allow re-establishment of baseline conditions, after which the medium was discarded and replaced with fresh buffer. After a further 30 min this buffer was exchanged and stored for analysis of baseline or time zero (T0) CK concentrations. The preparations were incubated for 30 min in the presence of suxamethonium $50 \text{ mmol litre}^{-1}$ (group S), 3% halothane (group H), suxamethonium $50 \text{ mmol litre}^{-1}$ and 3% halothane (group S+H) or without any additive, to serve as controls (group C). The pH of all materials added to the media was adjusted to 7.4 and checked using a Corning pH meter. The bathing medium was exchanged and replaced at the end of this time and stored for analysis as sample T30. The medium in each tube was changed at 30-min intervals for a further 60 min (samples T60 and T90), yielding a total of four samples for each preparation.

CK concentrations were measured spectrophotometrically on the same day as the experiment was performed, by measuring the catalysed conversion of NADP to NADPH at 340 nm. All chemicals were supplied by Sigma Chemical Company and were Anal-R grade.

Phase 2. After the completion of phase 1 experiments and analysis of the results, the combination of halothane-suxamethonium was adopted as the standard muscle "trauma". The purpose of this phase was to investigate the effect of chlorpromazine on enzyme efflux caused by the combination of suxamethonium and halothane. Muscle preparations were incubated as before, without any additions to the medium to serve as controls (group C), with suxamethonium $50 \text{ mmol litre}^{-1}$ and 3% halothane added to the gassing mixture from a calibrated Fluotec mark III vaporizer (group S+H) or suxamethonium, halothane and chlorpromazine $100 \mu\text{mol litre}^{-1}$ (group S+H+Ch). Replacement of the medium at 30-min intervals was performed as in phase 1, yielding four serial samples, and analyses of CK concentrations were performed promptly.

Under preset criteria, samples with a baseline CK activity of $> 50 \text{ u litre}^{-1}$ were removed

from analyses as they were thought to indicate occurrence of unacceptable muscle damage on dissection. Within each phase, the results were analysed statistically using two-factor repeated measures analysis of variance (ANOVA). $P < 0.05$ was considered significant.

RESULTS

A total of 70 muscle preparations yielded acceptable results in phase 1. The mean (SEM) baseline (T0) CK concentrations in the four groups were between 17.5 and $23.1 \text{ u litre}^{-1}$, with no significant difference between groups. In undamaged preparations, relatively little enzyme accumulated in the medium during this initial stabilizing period. CK concentrations remained constant or showed a slight tendency to decrease through each 30-min period (samples T30, T60 and T90) in groups C, H and S (fig. 1). In group S+H, CK values increased significantly in T30, T60 and T90 samples ($P < 0.05$ – 0.01). The mean CK concentration increased by a maximum of 157% (21 – 54 u litre^{-1}) at 60 min in this group.

A total of 48 muscle preparations yielded acceptable results in the second phase of the study. The baseline (T0) CK concentrations were comparable in the three groups and similar to baseline values in phase 1 of the study. The

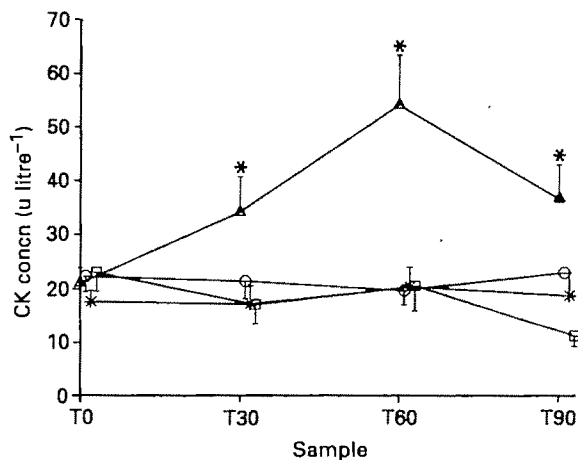


FIG. 1. Mean (SEM) CK concentrations with and without exposure to suxamethonium, halothane and their combination. ○ = control (group C) preparations ($n = 18$); □ = preparations exposed to suxamethonium (group S) ($n = 15$); X = preparations exposed to halothane (group H) ($n = 15$); △ = preparations exposed to suxamethonium and halothane (group H+S) ($n = 22$). * $P < 0.05$ compared with T0.

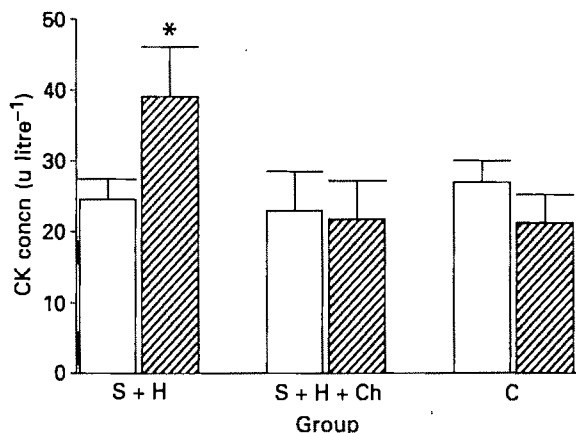


FIG. 2. Baseline (□) and maximal (▨) (SEM) CK concentrations in the presence of suxamethonium and halothane with or without chlorpromazine. C = Control preparations ($n = 18$); S+H = preparations exposed to suxamethonium and halothane ($n = 17$); S+H+Ch = preparations exposed to suxamethonium, halothane and chlorpromazine ($n = 13$). * $P < 0.05$ compared with respective baseline value.

maximal changes in CK in groups S+H and S+H+Ch are shown in figure 2. CK concentrations again, increased significantly in group S+H, this time by a maximum of 59% (24.6–39.1 u litre⁻¹), but showed only minimal and insignificant change in both the control (group C) and chlorpromazine-treated preparations (group S+H+Ch).

DISCUSSION

The measurement of efflux of cell-bound enzymes is an accepted method of assessing tissue damage in *in vivo* and *in vitro* preparations [4]. Isolated muscle preparations have been used with success in elucidating cellular processes involved in the pathogenesis of some muscle diseases [3, 6, 8, 11, 12]. The role of calcium and phospholipases, specifically phospholipase A2 (PLA2), in the cellular disruption associated with various muscle damaging processes has been identified from these studies. This enzyme may also have a role in the pathogenesis of malignant hyperthermia [13].

There are several problems associated with the use of an experimental model for the study of suxamethonium-induced muscle damage. The isolated muscle must be removed intact with minimal damage, the preparation must be suffic-

iently robust to maintain its integrity in an organ bath and the muscle membrane must depolarize in response to suxamethonium. The volume of the bathing medium in the organ bath must also be sufficiently small to measure the small changes in enzyme output. In addition, even though it is generally agreed that muscle damage is related to the depolarizing action of suxamethonium, there is considerable species variation in response of the muscles to the drug [14].

The biventer cervicis muscle of the chick, in common with the extraocular muscles, possesses fibres with multiple innervation and thereby responds to suxamethonium with sustained depolarization [15]. Significant enzyme release, however, is produced only when halothane is used concurrently, which is in keeping with the results in humans [16]. It is not known why this is so, but it is well documented that suxamethonium produces a decrease in serum concentration of calcium [17, 18], and suxamethonium has been suggested to produce muscle damage by causing an increase in myoplasmic calcium concentrations [5]. Increased cellular concentrations of calcium appear to stimulate membrane phospholipid degradation by activation of PLA2 [8, 19]. This process may lead to cellular damage by both production of damaging metabolites of arachidonic acid metabolism [7, 19] and generation of free radical species. In addition, halothane itself has been shown to decrease the threshold for calcium release from the sarcoplasmic reticulum [20], and produce inhibition of the intracellular enzyme InsP3-5ase, involved in the regulation of intracellular calcium concentration by degradation of the "second-messenger", inositol triphosphate [21]. It is possible and perhaps likely that halothane-induced increases in myoplasmic calcium may be the mechanism of its potentiation of muscle damage associated with suxamethonium.

Chlorpromazine, in the concentrations used in this experimental study, has been shown to inhibit the membrane destabilizing actions of PLA2 [10]. The possibility that suxamethonium in the presence of halothane produces enzyme efflux by PLA2 activation is supported by our finding that CK concentrations did not increase following this combination when chlorpromazine was added to the bathing medium. The protective action of chlorpromazine could also result from its ability to scavenge free radical species [22], or perhaps from a membrane stabilizing action.

It would be interesting to know if chlorpromazine prevents the contracture produced by suxamethonium in the presence of halothane, in addition to preventing the release of CK. This was not examined in the present investigation, which was designed to establish a model for the study of enzyme changes.

In conclusion, the chick biventer cervicis muscle appears suitable for investigating suxamethonium-induced muscle damage. The damage may be assessed by examining efflux of CK into a bathing medium. The increase in the enzyme was obtunded by addition of chlorpromazine to the medium before exposure to suxamethonium and halothane. It is possible that damage caused by suxamethonium is mediated by activation of the enzyme PLA2. In view of the effectiveness of chlorpromazine in the prevention of suxamethonium-induced CK efflux, and presumably muscle damage, it will be interesting to explore the effectiveness of this agent in preventing some of the side effects of suxamethonium in clinical situations.

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REFERENCES

1. Bourne JG, Collier HOJ, Somers GF. Succinylcholine (succinylcholine). Muscle relaxant of short action. *Lancet* 1952; 1: 1225-1229.
2. Tammisto T, Airaksinen M. Increase in creatine kinase activity in serum as a sign of muscular injury caused by intermittently administered suxamethonium during halothane anaesthesia. *British Journal of Anaesthesia* 1966; 38: 510-515.
3. Suarez-Kurtz G, Eastwood AB. Release of sarcoplasmic enzymes from frog skeletal muscle. *American Journal of Physiology* 1981; 241: C98-C105.
4. Jones DA, Newham DJ, Round JM, Tolfree SEJ. Experimental human muscle damage: morphological changes in relation to other indices of damage. *Journal of Physiology (London)* 1986; 375: 435-438.
5. McLoughlin C, Nesbitt GA, Howe JP. Suxamethonium induced myalgia and the effect of pre-operative administration of oral aspirin. *Anaesthesia* 1988; 43: 565-567.
6. Jones DA, Jackson MJ, Edwards RHT. Release of intracellular enzymes from an isolated mammalian skeletal muscle preparation. *Clinical Science* 1983; 65: 193-201.
7. Rodemann HP, Waxman L, Goldberg AL. The stimulation of protein degradation in muscle by Ca^{2+} is mediated by prostaglandin E_2 and does not require the calcium activated protease. *Journal of Biological Chemistry* 1982; 257: 8716-8723.
8. Duncan CJ. The role of phospholipase A2 in calcium induced damage in cardiac and skeletal muscle. *Cell and Tissue Research* 1988; 253: 457-462.
9. Ginsborg BL, Warriner J. The isolated chick biventer cervicis nerve-muscle preparation. *British Journal of Pharmacology* 1960; 15: 410-411.
10. Blackwell GJ, Flower RJ. Inhibition of phospholipase. *British Medical Bulletin* 1983; 39: 260-264.
11. Dawson DM. Efflux of enzymes from chicken muscle. *Biochimica et Biophysica Acta* 1966; 113: 144-157.
12. Publicover SJ, Duncan CJ, Smith JL. The use of A23187 to demonstrate the role of intracellular calcium in causing ultrastructural damage in mammalian muscle. *Journal of Neuropathology and Experimental Neurology* 1978; 37: 544-557.
13. Cheah KS, Cheah AM. Skeletal muscle mitochondrial phospholipase A2 and the interaction of mitochondria and sarcoplasmic reticulum in porcine malignant hyperthermia. *Biochimica et Biophysica Acta* 1981; 638: 40-49.
14. Zaimis E, Head S. Depolarising neuromuscular blocking drugs. In: Zaimis E, ed. *Neuromuscular Junction, Handbook of Experimental Pharmacology*, Vol 42. Berlin: Springer-Verlag, 1976; 365-419.
15. Bowman WC, Rand MJ. *Textbook of Pharmacology*, 2nd Edn. Oxford: Blackwell Scientific Publications, 1980; 17.1-17.53.
16. Charak DS, Dhar CL. Suxamethonium induced changes in serum creatine phosphokinase. *British Journal of Anaesthesia* 1981; 53: 955-957.
17. Collier CB. Suxamethonium pains and early electrolyte changes. *Anaesthesia* 1978; 33: 454-461.
18. Bourke DL, Rosenberg M. Changes in total serum Ca^{2+} , Na^{+} and K^{+} with administration of succinylcholine. *Anesthesiology* 1978; 49: 361-363.
19. Jackson MJ, Edwards RHT. Free radicals, muscle damage and muscular dystrophy. In: Quintanilla A, ed. *Reactive Oxygen Species in Chemistry, Biology and Medicine*. New York and London: Plenum Press, 1984; 197-210.
20. Nelson TE, Sweo T. Ca^{2+} uptake and Ca^{2+} release by skeletal muscle sarcoplasmic reticulum: Differing sensitivity to inhalational anesthetics. *Anesthesiology* 1988; 69: 571-577.
21. Foster PS, Gesini E, Claudianos C, Hopkinson KC, Denborough MA. Inositol 1,4,5-triphosphate phosphatase deficiency and malignant hyperpyrexia in swine. *Lancet* 1989; 2: 124-126.
22. Smith DS, Rehncrona S, Siesjö BK. Inhibitory effect of different barbiturates on lipid peroxidation in brain tissue *in vitro*: comparison with the effects of promethazine and chlorpromazine. *Anesthesiology* 1980; 53: 186-194.

COMPARISON OF CONTEMPORANEOUS AND RETROSPECTIVE ASSESSMENT OF POSTOPERATIVE PAIN USING THE VISUAL ANALOGUE SCALE

W. H. D. LIU AND A. R. AITKENHEAD

SUMMARY

We have assessed postoperative pain in 50 patients who had undergone total abdominal hysterectomy, using repeated contemporaneous and single retrospective visual analogue scores. There were significant correlations between the median, mean and greatest contemporaneous scores, and the single retrospective scores, but there was a wide scatter of results among and within individual patients. We conclude that the wide variability between the two methods of assessment suggests that the two techniques should not be used interchangeably.

KEY WORDS

Measurement techniques: visual analogue scale, retrospective. Pain: postoperative.

The visual analogue scale (VAS) is used commonly to quantify pain in clinical investigations. However, the frequency and timing of pain assessment in the postoperative period vary considerably and are often selected empirically. For instance, pain may be assessed hourly or at specific times such as during mobilization. In the past, some investigators used a single retrospective measurement to assess the intensity of pain in the preceding 24 or 48 h [1, 2]. However, the reliability of assessing pain using this type of single retrospective assessment has not been compared with repeated contemporaneous assessment. The purpose of this study was to compare these two methods of assessment.

PATIENTS AND METHODS

We studied 50 healthy patients who had undergone total abdominal hysterectomy; all received a standard general anaesthetic. They were pre-

medicated with temazepam 10–20 mg and anaesthesia was induced with thiopentone 5 mg kg⁻¹ and fentanyl 1.5–2 µg kg⁻¹. Tracheal intubation was facilitated with vecuronium 0.1 mg kg⁻¹ and the patient's lungs were ventilated with 67% nitrous oxide and 0.5–1.5% enflurane in oxygen. At the end of the operation, residual neuromuscular block was antagonized with neostigmine 35 µg kg⁻¹ and glycopyrronium 8 µg kg⁻¹. None of the patients received regional analgesia. I.m. injections of papaveretum 0.2–0.3 mg kg⁻¹ were prescribed 4-hourly and administered when deemed to be required, by the nursing staff.

The principle of the visual analogue scale was explained to all patients on the day before the operation. The VAS consisted of a 100-mm line on A4 paper, with "No pain at all" printed on the extreme left of the line and "Worst possible pain" on the right. Pain was assessed by the patients every 2 h on the first day after operation from 09:00 to 21:00. As a result, there were seven pain scores for each patient on the first day. These represented the contemporaneous scores; the median, mean and the greatest value of these scores were used for subsequent analysis. A new VAS was used for each assessment and patients were unable to refer to their previous scores. At 09:00 on the second day, two further VAS were completed. The first assessed the overall pain of each patient in the preceding 24 h; this represented the single retrospective score. The second assessed the severity of the patient's current pain. The analgesic requirement during the period of assessment was also recorded.

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RESULTS

The mean age (range) and weight (SD) of the patients were 42.3 (26–65) yr and 64.6 (8.1) kg, respectively. The mean (SD) dose of papaveretum administered on the first day after operation was

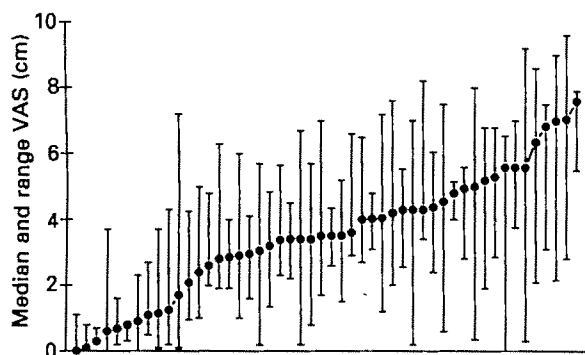


FIG. 1. Median (●) and range (bars) of VAS for all patients, arranged in ascending order of median values.

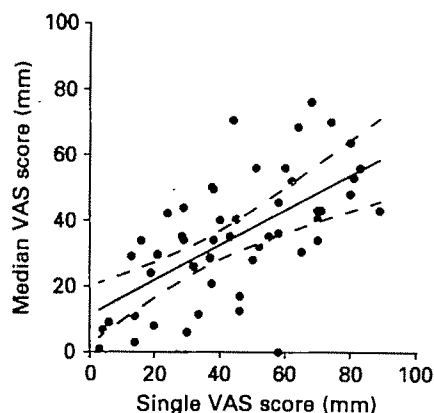


FIG. 2. Relationship between the median VAS score and single retrospective VAS score. The solid line represents the regression line and the interrupted lines represent the 95% confidence intervals of the regression line.

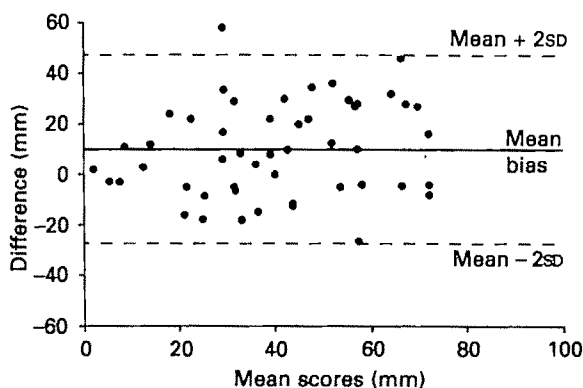


FIG. 3. Relationship between the mean of the median plus retrospective VAS (Mean scores) and the difference (retrospective minus median) between the scores (Difference). The dotted line represents the mean bias, the two interrupted lines represent the limits of agreement.

24.3 (12.3) mg. The distribution of the median and range of contemporaneous scores for all patients is shown in figure 1. It is clear that there was wide variability of pain scores both within and between patients.

The relationship between the single retrospective score and the median contemporaneous score is shown in figure 2. There was a significant correlation between them ($r = +0.63$, $P < 0.0001$). Similar relationships were found between the single retrospective score and the mean contemporaneous score ($r = +0.63$, $P < 0.0001$), and between the single retrospective score and the greatest contemporaneous score ($r = +0.66$, $P < 0.0001$). The correlations between the single retrospective score and the smallest contemporaneous score or the contemporaneous scores at 09:00 on the second day were weaker ($r = +0.31$ and $+0.56$, respectively), but were also statistically significant. The Y-intercept and the slope of the regression line between the single retrospective and the various contemporaneous scores are summarized in table I.

TABLE I. Relationships between single retrospective and contemporaneous (mean, median, current pain at 09:00 on second day, smallest and greatest) scores

VAS	<i>r</i>	<i>P</i>	Intercept (95% C.I.)	Slope (95% C.I.)	Residual SD	Mean bias (2SD)
Mean	0.63	< 0.0001	14.2 (5.5–22.9)	0.47 (0.25–0.69)	13.1	9.8 (35.8)
Median	0.63	< 0.0001	11.2 (2.3–20.1)	0.53 (0.31–0.75)	14.9	9.9 (36.6)
09:00 second day	0.56	< 0.0001	3.4 (–5.1 to 11.9)	0.55 (0.31–0.79)	18.5	17.1 (42.4)
Smallest	0.31	< 0.028	7.5 (2.0–13.0)	0.18 (–0.09 to 0.45)	12.4	29.6 (45.2)
Greatest	0.66	< 0.0001	26.6 (13.7–39.5)	0.64 (0.42–0.85)	16.7	–10.2 (37.4)

The data were analysed also using Bland and Altman's method [3] in order to examine the agreement between the two approaches of pain assessment. The mean bias and limits of agreement are the mean and $\pm 2SD$, respectively, of the differences between two methods of measurement. In the case of the single retrospective scores and the median contemporaneous scores, the mean bias and limits of agreement were 9.9 mm and ± 36.6 mm, respectively (fig. 3). The mean biases and the limits of agreement between the retrospective scores and the various contemporaneous scores are also summarized in table I.

DISCUSSION

Pain is a subjective sensation and is difficult to measure. Nevertheless, it is important to quantify it as reproducibly as possible. It has been stressed again recently that pain should be assessed routinely in the postoperative period, with other physiological variables such as arterial pressure and heart rate [4]. There is a range of methods available, but the frequency and timing of pain assessments vary considerably. Multidimensional assessment, for example the McGill pain questionnaire, has been shown to produce consistent results, but is probably too complicated to use in the immediate postoperative period. In contrast, visual analogue scales are easy to use and have been utilized widely by clinical investigators to quantify acute pain in the postoperative period. Moreover, the reliability and reproducibility of VAS have been studied extensively [5, 6].

In the past, single retrospective assessment has been used to assess acute postoperative pain [1, 2]. The potential advantages of a single retrospective assessment of overall pain are that it is less labour-intensive, more convenient to the investigators and less disruptive to the patients. It may also allow prediction of some feature of the contemporaneous scores (i.e. the mean, median, greatest or smallest). In addition, factors such as the residual effect of general anaesthetics and the sedation associated with opioid drugs, which may increase the variability of pain perception and its measurement, may be greatly reduced by using a single retrospective assessment. However, the use of a single retrospective assessment of the overall pain relief in the preceding 24 h has been criticized [7, 8]. In addition, it has been reported that patients were unable to remember severe pain in the immediate postoperative period when

questioned the following day [9]. In a study [10] which examined the analgesic effect of nalbuphine, patients were reported to have severe pain and high contemporaneous pain scores, but these patients reported good or excellent overall pain relief retrospectively at the end of the study. Retrospective assessment of labour pain [11] and chronic pain [12] have been investigated; parturients appeared to have lower retrospective scores [11], whereas patients with chronic pain tended to report higher retrospective scores [12], but the methods of analysis were different from those used in the present study. However, no formal comparison of contemporaneous and retrospective scoring has been carried out previously.

The highly significant correlations between the single retrospective scores and the median, mean and greatest contemporaneous scores were not surprising, as the contemporaneous and retrospective scores were measuring approximately the same variable. In general, patients might be expected to have a better memory of their worst pain (highest scores) than their least pain (lowest scores), as reflected by the greater correlation coefficient for the former. The correlation between the single retrospective score and the current pain score at 09:00 on the second day was relatively weak, suggesting that pain at the time of retrospective assessment may have little influence on the memory of overall pain on the previous day. However, correlation coefficient only measures the strength of relation between two variables and not the agreement of the relation between them.

According to Bland and Altman [3], it is more informative to plot the difference of the measurements by the two methods against the mean of these measurements. The mean bias represents the mean of the differences between the two scores for all patients. The limits of agreement represent 2 SD of these differences from the mean bias. In this study, the single retrospective scores tended to be greater than the median contemporaneous scores by 9.9 mm (mean bias), but the limits of agreement were wide (± 36.6 mm). The scatter of results is too wide for the two methods to be used interchangeably, and therefore it is probably too unreliable to predict the median contemporaneous scores from the single retrospective scores. Similar wide limits of agreement were found between the single retrospective scores and the other contemporaneous scores.

It has been suggested that analgesics with

amnesic properties might provide misleading results if studies depended on retrospective assessments [10]. In addition, the mode of administration of analgesic drugs may have an influence on the variability of pain perception, depending on the elapse of time between drug administration and pain assessment; intermittent i.m. injections may increase the variability of pain assessment in comparison with continuous infusions, patient-controlled analgesia or administration of analgesics via the extradural route. As a result of the wide scatter of data and wide limits of agreement between the retrospective and contemporaneous scores, we conclude that the two methods of acute pain assessment cannot be used interchangeably in the postoperative period when the administration of opioids is via intermittent i.m. route. The implication of this is that studies on acute pain and its management may be compared with each other only if the same method of pain measurement has been used.

ACKNOWLEDGEMENT

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REFERENCES

1. White WD, Pearce DJ, Norman J. Postoperative analgesia: a comparison of intravenous on demand fentanyl with epidural bupivacaine. *British Medical Journal* 1979; 2: 166-167.
2. Fell D, Chmielewski A, Smith G. Postoperative analgesia with controlled-release morphine sulphate: comparison with intramuscular morphine. *British Medical Journal* 1982; 285: 92-94.
3. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307-310.
4. *Report of the Working Party on Pain after Surgery. Commission on the Provision of Surgical Services*. London: The Royal College of Surgeons of England and the College of Anaesthetists, 1990; 7-8.
5. Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976; 31: 1191-1198.
6. Banos JE, Bosch F, Canellas M, Bassols A, Ortega F, Bigorra J. Acceptability of visual analogue scales in the clinical setting: a comparison with verbal rating scales in postoperative pain. *Methods and Findings in Experimental and Clinical Pharmacology* 1989; 11: 123-127.
7. Kay B. Relative potency of agonist and partial agonist opioids. *British Journal of Anaesthesia* 1985; 57: 718.
8. Smith G. Clinical trials of analgesic drugs. In: Harmer M, Rosen M, Vickers MD, eds. *Patient Controlled Analgesia*. Oxford: Blackwell Scientific Publications, 1985; 53.
9. Pugh GC, Drummond GB, Elton RA, Macintyre CGA. Constant i.v. infusions of nalbuphine or buprenorphine for pain in patients following abdominal surgery. *British Journal of Anaesthesia* 1987; 59: 1364-1374.
10. Pugh GC, Drummond GB. A dose-response study with nalbuphine hydrochloride for pain in patients after upper abdominal surgery. *British Journal of Anaesthesia* 1987; 59: 1356-1363.
11. Norvell KT, Gaston-Johansson, Fridh G. Remembrance of labor pain: how valid are retrospective pain measurement? *Pain* 1987; 31: 77-86.
12. Linton SJ, Melin L. The accuracy of remembering chronic pain. *Pain* 1982; 13: 281-285.

ANAESTHESIA FOR PATIENTS WITH TRANSPLANTED HEARTS AND LUNGS UNDERGOING NON-CARDIAC SURGERY

I. H. SHAW, A. J. B. KIRK AND I. D. CONACHER

Organ transplantation has become an established form of surgical management in a patient with selected end-stage chronic disease not amenable to conventional medical or surgical treatment. Heart and lung transplantation is performed by a few National centres in the United Kingdom often some distance from the patient's home. The national figures for cardiopulmonary transplantation in the United Kingdom and Eire during 1989, as notified to Transplant U.K., were: heart 302; heart-lung 94; lung 39. Worldwide, 2450 transplantations were performed during 1988 [15].

Medical attendants should be alert to recognizing problems caused by the presence of infection in immunosuppressed patients, modes of presentation of rejection phenomena and how transplanted organs, notably significantly denervated ones, may behave and respond under the pathophysiological circumstances that arise during surgery, resuscitation and intensive care.

BACKGROUND

Type of transplant

Heart. Heart transplantation is suitable only for a highly selected group of patients in end-stage cardiac failure, the majority of whom suffer from ischaemic heart disease or cardiomyopathy [15]. Contraindications vary from centre to centre. Relative contraindications and risk factors include: age more than 60 yr; increased pulmonary vascular resistance; peripheral vascular disease; diabetes mellitus; neoplastic disease; renal dysfunction; hepatic disease; acute infection; multi-

system disease; adverse social conditions; adverse psychiatric conditions.

The International Society for Heart Transplantation reported that 83% of patients are male in the age range 34-55 yr.

The diseased heart is removed during bypass, leaving right and left atrial remnants. Consequently, the postoperative ECG may exhibit two P waves [12]. The impulse generated by the atrial remnant is inconsequential.

Combined heart-lung (HLT). Originally applied to primary pulmonary hypertension and Eisenmengers' Syndrome, HLT has expanded to include parenchymal lung diseases, predominantly septic lung conditions such as cystic fibrosis and bronchiectasis. Generally, patients undergoing HLT are younger than those having heart transplants, with a mean age of 29 yr.

Single lung (SLT). SLT is performed for isolated pulmonary disease with minimal cardiac involvement. Since the first successful SLT was performed in 1983, it has developed as an acceptable surgical treatment for suitable patients in respiratory failure. Most experience to date has been with pulmonary fibrosis, but the indications are widening on an experimental basis to include emphysema and pulmonary vascular diseases.

Where appropriate, SLT has several advantages in comparison with HLT. Three recipients can benefit from a single organ donor. This is particularly important as the number of patients awaiting transplantation increases. Cardiopul-

KEY WORDS

Heart: heart-lung transplantation. Surgery: non-cardiac.

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TABLE I. *Survival rates of patients who underwent heart, heart-lung and lung transplantation*

Organ transplanted	Survival	%	Source
Heart-lung	30 days	81.2	[15]
	1 year	55.7-61.1	[15]
	5 year	55.4	[15]
Heart	30 days	91.1	[15]
	5 year	73.9-81.9	[15]
	10 year	73.3	[15]
Lung	1 year	65.0	[J. D. Cooper, personal communication]

monary bypass is often not necessary for SLT [6]. In some centres, previous thoracotomy or pleurodesis is a contraindication to HLT because of the hazards of bleeding. At the Freeman Hospital we prefer not to accept patients with a previous thoracotomy or pleurodesis for SLT, but these are not absolute contraindications. The avoidance of cardiopulmonary bypass reduces the extent of postoperative bleeding. In SLT the carina remains innervated, which facilitates the patient's own cough reflex. There is also less obliterative bronchitis in SLT, although this has not been validated. Finally, in the event of rejection after SLT, the contralateral lung should be able to provide acceptable support.

Double lung (DLT). The initial experience with DLT involved transplanting both lungs *en bloc* with a left atrial anastomosis, pulmonary artery anastomosis and a single tracheal anastomosis. There were major problems with tracheal healing, leading to dehiscence and stenosis. Consequently, this technique was abandoned. However, the concept of sequential single or bilateral lung transplantation was developed whereby two lungs are implanted separately via a sternotomy or bilateral thoracotomies. This is much more promising and allows the patient to keep his own heart. DLT is restricted to a few centres, but may in time prove to be of value in septic conditions such as cystic fibrosis.

Survival

Better patient selection, improved surgical and anaesthetic techniques and the introduction of cyclosporin as part of triple immunosuppressive regimens have led to improved survival for transplant patients. The first year after transplantation appears to be the most critical, with the greatest mortality, particularly from rejection and

infection. The nature of the immunosuppressive regimen seems to have an influence on survival; those receiving corticosteroids, azathioprine and cyclosporin have the best outcome. The sex and age of the patient do not appear to be significant factors. Table I gives the current survival rates for cardiopulmonary transplantation.

Morbidity and mortality

Recipients of transplanted hearts and lungs are prone to several major problems, the foremost of which are organ rejection and opportunistic infection. Rejection is discussed later.

Arrhythmias. An increased frequency of arrhythmias after cardiac transplantation has been reported by several workers [1, 14], in particular, ventricular premature beats. Exercise has been demonstrated to increase the frequency of arrhythmias [29].

Providing the heart functions well, and in the absence of rejection, these arrhythmias are thought to be benign. However, ventricular tachycardia has been reported also and may be responsible for sudden death in patients with transplants [24]. Several mechanisms have been postulated for these frequent arrhythmias, including hypersensitivity to circulating catecholamines, loss of vagal tone and ischaemia secondary to graft coronary atherosclerosis [29].

Infection. Infection presents a major risk to immunosuppressed patients and is a significant cause of morbidity and mortality [15]. In one series [12], it was reported that 16 of 33 patients who had undergone heart transplantation died from infection.

Infections seem to be commonest during the first 3 months after transplantation [8, 13]. The lung is the organ affected most commonly. A multitude of micro-organisms have been isolated, but the most common viral agents are *Cytomegalovirus* and *Herpes simplex*. Protozoal and fungal infections also occur, most notably *Pneumocystis carinii* pneumonia.

The incidence of opportunistic infection appears to decline 6 months after transplantation [22], but as long as the patient continues to receive immunosuppressants and corticosteroids, the risk of infection persists.

Neoplasia. Immunosuppressed patients are known to have a greater incidence of malignant

neoplasms [23] and lymphoma [25] than the general population. Cardiac transplant patients appear to be at a greater risk in this respect compared with renal transplant patients, possibly because the former have a more intense immunotherapy regimen [20]. A second transplantation appears to enhance further the risk of subsequent malignancy [13].

Psychological problems. Psychological problems associated with organ transplantation have been reviewed [18]. In general, the psychological status of most patients improves after cardiac transplantation, although transient psychiatric disorders are not uncommon in the early post-operative period [10]. Organic mental disorders were the most frequent observation and thought to be associated with drug therapy or other metabolic derangements. Chronic psychiatric conditions such as anxiety and depression occur and appear to correlate with preoperative psychological status. Depression and anxiety may lead to non-compliance with drug therapy, a problem shared by many chronically ill patients. Drug non-compliance is thought to be a significant factor in many cases of organ rejection.

Nature of the presenting illness

Isolated reports of anaesthesia in patients with transplanted hearts have appeared in the literature for a wide variety of non-cardiac procedures including total hip replacement, laparotomy, removal of infected toe nails, aortic aneurysm repair and lumbar laminectomy [2, 7, 9, 19, 28].

Steed and colleagues [30] noted a greater incidence of general surgical complications in post-transplant patients compared with other post-cardiopulmonary bypass patients, and that these complications were associated with a greater than expected mortality rate. Colon and colleagues [4] reported that biliary and pancreatic disorders were a common cause of surgical intervention in post-transplant patients. An increased risk of serious complications was noted also in those patients who underwent surgery.

Because of the smaller number of successful lung transplants, reports in the literature of subsequent anaesthesia are uncommon unless associated with a heart transplant.

REJECTION

Heart

Acute allograft rejection is a serious compli-

cation in the post-transplantation period and a major cause of mortality and morbidity [15]. The long-term results of heart transplantation are marred by the complication of accelerated coronary atheroma, thought to be a manifestation of chronic rejection. In one series [13], it was reported that 46% of transplant patients had angiographic evidence of graft coronary artery disease 2 years after transplantation, increasing by a further 1% after 4 years. Graft atherosclerosis is not infrequently associated with haemodynamic abnormalities.

The patient with the denervated heart does not experience angina or cardiac chest pain, the usual hallmarks of myocardial ischaemia. The only warning of impending rejection or ischaemia may be a complaint of excessive tiredness and dyspnoea which in time may manifest as heart failure [3]. Therefore, it is policy in most units to perform coronary angiography on an annual basis. Atrial arrhythmias were observed in 40% of patients during an episode of rejection, the frequency declining in response to antirejection therapy. Bradycardia and small ECG complexes should also alert the physician to the possibility of impending rejection, as should an increased frequency of transient ischaemic attacks [17].

Lungs

Early lung transplants were troubled with rejection and breakdown of the bronchial anastomosis, usually within 4 weeks of transplantation. This has been overcome partially by the technique of wrapping a pedicle of omentum, pulled through a hole in the diaphragm, around the anastomosis. The omentum appears to promote revascularization of the bronchus distal to the anastomosis [6]. The steroid sparing effect of cyclosporin A has also had a beneficial effect on healing.

Detecting rejection of a transplanted lung can often be difficult, as the symptoms may mimic those of a chest infection. Typically, rejection is associated with fatigue, dyspnoea, sudden arterial desaturation, pyrexia and leucocytosis. Perihilar infiltration or graft opacification on the chest x-ray [5, 32] may be preceded by a decrease in D_1CO and FEV_1 [16]. Pulmonary blood flow decreases as detected by isotope perfusion scan [6]. Although these non-invasive investigations are useful indicators, it is imperative to differentiate between infection and rejection using the relatively simple techniques of bronchoalveolar lavage and transbronchial lung biopsy. The

predominant pathological finding in acute lung rejection is of perivascular or peribronchial infiltration by mononuclear cells.

Heart-lung

Heart-lung allograft rejection is similar to that described for the individual organs. In practice, pulmonary rejection precedes cardiac rejection and it is rare for cardiac rejection to occur in the absence of lung rejection.

Obliterative bronchiolitis appears to be more common in lungs which have rejected when the transplant was in conjunction with a heart transplant than in isolated lungs [6].

If the anaesthetist suspects an episode of rejection, surgery should be postponed and the patient referred to the transplantation centre, as anaesthesia in the presence of ongoing rejection presents formidable management problems and may necessitate full inotropic and mechanical support.

DENERVATION

Heart

Physiology. The physiology of the transplanted heart has been discussed by several authors [9, 12, 26]. The denervated heart has a greater resting rate in the absence of vagal tone, generally 90–100 beat min⁻¹. No autonomic reinnervation takes place in humans after transplantation, therefore the normal sympathetic responses to laryngoscopy and intubation are absent. The heart does respond to circulating catecholamines, although this response may take 5–6 min to manifest. The normal baroreceptor reflexes are absent and carotid sinus massage and Valsalva manoeuvre have no effect on heart rate.

Of concern to the anaesthetist is the absence of tachycardia in response to light anaesthesia or hypovolaemia. Increases in cardiac output are achieved by increasing stroke volume rather than heart rate. Modulation of cardiac output is dependent, therefore, on intrinsic mechanisms. The anaesthetized patient with a heart transplant may show exaggerated responses to hypovolaemia, sudden changes in posture or decreases in systemic vascular resistance. Care should be taken, therefore, to avoid excessive loss of volume, dehydration or significant peripheral vasodilatation. Consequently, it is desirable to maintain an adequate preload at all times.

Pharmacology. In the denervated heart, drugs

with autonomic activity, such as atropine, neostigmine, suxamethonium and pancuronium, have little effect on heart rate. Glucagon and digitalis exhibit inotropic effects, although the latter has no significant influence on heart rate or AV nodal conduction [21, 24, 26]. The heart receptors remain responsive to drugs, and sympathomimetic amines such as isoprenaline, adrenaline, dopamine and dobutamine respond in the normal manner.

Reflex tachycardia, often seen with vasodilator drugs such as hydralazine, glycerin trinitrate and sodium nitroprusside is absent and hypotension may be exaggerated.

Anti-arrhythmic drugs act in the normal manner and cardioversion remains effective.

Lung

Physiology. The transplanted lung is denervated distal to the bronchial anastomosis. Modulation of the mechanics of breathing is regarded generally as being under brainstem control, and respiratory and apneustic centres receive peripheral information from chemo- and stretch receptors via the vagus nerve. As with the denervated heart, no functional reinnervation takes place. Rhythmic disturbances of breathing have been reported in the early postoperative period, but the normal pattern appears to return quickly [27]. The lung responds normally to exercise and carbon dioxide.

Several workers have described transient reduction in lung volume secondary to changes in the rib cage and vertebral column [16]. The FEV₁ increases progressively to reach preoperative values by 6 months [31].

Of concern to the anaesthetist is the cough reflex. This is initiated by stimulation of receptors in the trachea, bronchi and bronchioles. Stimulation of any airway distal to the anastomosis does not elicit a cough reflex. In single lung transplants, the carina remains intact, consequently carinal stimulation elicits a cough reflex. Extubation of the trachea of lung transplant patients should be delayed until the patient is sufficiently awake to co-operate and respond to verbal commands to cough. Expectoration from the transplanted lung has to be encouraged by postural drainage and physiotherapy.

Although regarded as having some advantages over heart-lung transplants [6], single lung transplants give rise to an imbalance of perfusion. The transplanted lung is often perfused preferentially by virtue of its lesser vascular resistance compared with the remaining diseased lung. Anaesthesia should therefore avoid manoeuvres that give rise

TABLE II. *Postoperative modulation of immunosuppression therapy in transplant patients undergoing surgery unable to take medication orally*

Before operation		After operation		
Drug	Route	Drug	Route	Notes
Prednisolone	Oral	Methylprednisolone	I.v.	Given at a ratio of 0.8 of the dose of prednisolone
Azathioprine	Oral	Azathioprine	I.v.	Given as the same dose as orally
Cyclosporin	Oral	Cyclosporin	I.v.	Given as 25% of the oral dose over 6 h twice daily at 08.00 and 20.00. Monitor blood concentrations

to excessive increases in pulmonary vascular resistance.

Pharmacology. It has been noted that some heart-lung transplant patients have an increased Pa_{CO_2} in the postoperative period. In time, the Pa_{CO_2} decreases to within normal limits. In animals, vagotomy has been shown to reduce the ventilatory response to hypercapnia. Finch and Jamieson [9] have expressed fears that drugs which depress ventilation may further obtund the response to carbon dioxide. The clinical significance of this observation is not clear.

Despite denervation, bronchoconstriction has been described in a patient with a transplanted lung which subsequently rejected [9]. Interestingly, there was a poor response to bronchodilators such as isoprenaline, aminophylline and adrenaline.

DRUG THERAPY

Heart and lung transplant patients receive a wide variety of drugs, many of which are familiar to the anaesthetist. The complex drug regimens are essential for the maintenance of the allograft. In addition to immunosuppressive drugs such as azathioprine, cyclosporin and corticosteroids, these patients are often receiving antihypertensive agents, diuretics, histamine-2 blockers, antifungal and antiviral agents. A full discussion of these drugs is beyond the scope of this article, but several points are of concern to the anaesthetist in relation to cyclosporin A, the cornerstone of antirejection therapy.

Cyclosporin A has been reported to have a wide variety of drug interactions and side effects, particularly nephrotoxicity and hepatotoxicity. In one study after heart transplant, all patients receiving cyclosporin A demonstrated chronic

nephrotoxicity within 2 years of transplantation [13]. Hypertension is associated not infrequently with nephrotoxicity. In experimental animals, cyclosporin infusions have been shown to potentiate the neuromuscular blocking effects of atracurium and vecuronium. Cremophor EL, the solubilizing agent of cyclosporin, further enhanced this effect [11]. The clinical significance of this finding is uncertain.

Preoperative drug therapy

All medication should be continued as prescribed up to the day of operation. This is essential for immunosuppressive therapy. A supplementary dose of steroids is given usually during anaesthesia.

Postoperative drug therapy

After operation, the drug regimen should continue. Where possible, medication should be given orally. Following gastrointestinal surgery, or when the patient is unable to take enteral medication, modulation of the immunosuppressive regimen is necessary (table II). It is our practice to continue steroids i.v. as methylprednisolone in an equivalent dose. Azathioprine may be given i.v. at the same dose as given orally. Changes in cyclosporin dose necessitate monitoring blood concentrations after operation in order to maintain them within the therapeutic range of 150–250 mg ml⁻¹.

PREOPERATIVE EVALUATION

The approach to the preoperative assessment of a patient with a transplanted heart or lung should not differ from that of any other patient. Transplant patients are issued with a record book which provides the anaesthetist with the latest infor-

mation obtained at the last hospital visit. The record notes details of drug therapy, biopsy results, electrocardiograms, chest x-rays and any other relevant details, including the phone number of the transplant centre. Early communication with the transplant centre is desirable, particularly regarding any perioperative changes in immunosuppressive therapy.

The usual preoperative investigations should be conducted: review patient's record book; perform full blood count; measure haemoglobin, urea, electrolyte and creatinine concentrations; perform liver and pulmonary function tests; chest x-ray; ECG; sputum microbiology. If an in-dwelling pacemaker has been fitted, the usual assessment of its function should be made.

ANAESTHETIC TECHNIQUE

After the patient is assessed before operation and it has been established that there is no rejection, the patient should be premedicated with the usual premedication of choice.

A wide variety of general anaesthetic techniques have been described in the literature, all of which have been successful. In general, an i.v. induction followed by tracheal intubation and ventilation using a neuromuscular blocking agent, an opioid and an inhalation agent, or spontaneous breathing with an inhalation agent, seem to be the most popular.

Several authors have expressed concern at the use of spinal or extradural anaesthesia in cardiac transplant patients because of exaggerated hypotensive responses [2,9]. Firestone [personal communication] has reviewed 127 post-transplant procedures and found that 20% were performed under regional anaesthesia and 30% under i.v. sedation. Recently, we have used extradural anaesthesia for postoperative pain control over a 2-day period in a post cardiac transplant patient who had undergone oesophagogastrrectomy. The patient was hydrated adequately and changes in haemodynamic state were minimal.

All peripheral, central and arterial cannulae should be sited under full aseptic techniques. Disposable sterile tracheal tubes should be used and all i.v. infusions fitted with bacterial filters and injection ports kept capped and sterile.

Of greatest concern is the development of perioperative bradycardia in a patient with a transplanted heart. As atropine is ineffective in increasing heart rate, an infusion of isoprenaline

should be readily available for administration through a peripheral cannula.

In patients with isolated lung allografts, care should be taken to avoid excessive airway pressures which may stress the bronchial anastomosis. A transplanted lung is deprived of lymphatic drainage and great care should be taken to avoid fluid overload in these patients. It has been postulated [19] that potentially noxious stimuli, such as prolonged increased oxygen concentrations, may be deleterious to the graft.

Appropriate antibiotic cover is essential in all transplant patients undergoing surgery. The normal regimen used for non-transplant patients should be adopted, the choice of antibiotic prophylaxis being dictated by the nature of the surgery. It is prudent also to include a single dose of an anti-staphylococcal agent, such as flucloxacillin, to cover the insertion of all percutaneous cannulae.

Monitoring

Standard perioperative monitoring of the ECG, arterial pressure, oxygen saturation and end-tidal carbon dioxide concentration may be all that is required in a well patient. The nature of the perioperative monitoring should be decided after consideration of the patient's preoperative condition and the proposed surgery.

The risk of infection is such that the use of invasive monitoring should be avoided unless it is felt to be absolutely necessary. When central venous pressure monitoring is necessary, the catheter should be inserted via the antecubital fossa or the left internal jugular vein, as routine cardiac biopsies are performed usually via the right internal jugular vein.

POSTOPERATIVE CARE

Postoperative care should be routine, but extra vigilance should be exerted to detect infection. Any evidence of infection must be investigated early and treated accordingly. Fluid balance must be monitored carefully to avoid excessive positive balances, particularly in patients with transplanted lungs. Lung transplant patients should be encouraged to cough and expectoration promoted by physiotherapy and postural drainage where possible.

SUMMARY

Heart and lung transplantation is now accepted as

a means of treating some end-stage cardiopulmonary diseases. These patients may present with a wide variety of non-cardiopulmonary conditions requiring anaesthesia and surgery, possibly at a place distant from their original transplant centre. In general, for much elective, acute or even emergency surgery, if the allograft is functioning satisfactorily, these patients should present few problems during anaesthesia, provided the anaesthetist has some understanding of the pathophysiology of the transplanted organ and recognizes the differences (potential and specific to cardiopulmonary transplantation) between such patients and any other subject.

REFERENCES

- Berke DK, Graham AF, Schroeder JS, Harrison DC. Arrhythmias in the denervated transplanted human heart. *Cardiovascular Surgery* 1973; 47 and 48: 112-115.
- Bricker SRW, Sudgen JC. Anaesthesia for surgery in a patient with a transplanted heart. *British Journal of Anaesthesia* 1985; 57: 634-637.
- Chomette G, Aurio M, Cabrol C. Chronic rejection in human transplantation. *Journal of Heart Transplantation* 1988; 7: 292-297.
- Colon R, Frazier OH, Kahan BD, Radovancevic B, Duncan JM, Lorber MI, Van Buren CT. Complications in cardiac transplant patients requiring general surgery. *Surgery* 1988; 103: 32-38.
- Conacher ID. Isolated lung transplantation: A review of problems and guide to anaesthesia. *British Journal of Anaesthesia* 1988; 61: 468-474.
- Dark J, Cooper JD. Transplantation of the lungs. *British Journal of Hospital Medicine* 1987; 35: 443-445.
- Eisenkraft JB, Dimich I, Sachdev VP. Anaesthesia for major non-cardiac surgery in a patient with a transplant. *Mount Sinai Journal of Medicine* 1981; 48: 116-120.
- Emery RW, Icenogle T, Copeland JG. Managing the cardiac transplant patient. In: Brown RR, ed. *Anaesthesia and Transplantation Surgery*. Philadelphia: F. A. Davies, 1989; 73-90.
- Finch EL, Jamieson SW. Anaesthesia for combined heart and lung transplantation. In: Brown RR, ed. *Anaesthesia and Transplantation Surgery*. Philadelphia: F. A. Davies, 1989; 109-131.
- Freeman AM, Folks DG, Sokal RS, Fahs JJ. Cardiac transplantation: Clinical correlates of psychiatric outcome. *Psychosomatics* 1988; 29: 47-54.
- Gramstad LL, Gjerlow JA, Hysing ES, Rugstad HE. Interaction of cyclosporin and its solvent Cremophor with atracurium and vecuronium. *British Journal of Anaesthesia* 1986; 58: 1149-1155.
- Grebenik CR, Robinson PN. Cardiac transplantation at Harefield. *Anaesthesia* 1985; 40: 131-140.
- Hakin M, Wallwork J, English T. Cyclosporin A in cardiac transplantation: Medium-term results in 62 patients. *Annals of Thoracic Surgery* 1988; 46: 495-501.
- Harrison DC, Mason JW, Schroeder JS, Stinson EB. Effects of cardiac denervation on cardiac arrhythmias and electrophysiology. *British Heart Journal* 1978; 40 (Suppl.): 17-23.
- Heck CF, Shumway SJ, Kaye MP. The Registry of the International Society for Heart Transplantation: Sixth Official Report—1989. *Journal of Heart Transplantation* 1989; 8: 271-276.
- Higginbottom T. Physiology of the transplanted lungs and results. In: Wallwork J, ed. *Heart and Lung Transplantation*. Philadelphia: W. B. Saunders, 1989; 533-544.
- Hotson JR, Pedley TA. Neurological complications of cardiac transplantation. *Brain* 1976; 99: 673-694.
- House RM, Thompson TL. Psychiatric aspects of organ transplantation. *Journal of the American Medical Association* 1988; 260: 535-539.
- Kanter SF, Samuels SI. Anaesthesia for major operations on patients who have transplanted hearts. A review of 29 cases. *Anesthesiology* 1977; 46: 65-68.
- Lanza RP, Cooper DKC, Cassidy MJD, Barnard CN. Malignant neoplasms occurring after cardiac transplantation. *Journal of the American Medical Association* 1983; 249: 1746-1748.
- Leachman RD, Cokkinos DVP, Cabrera R, Leatherman LL, Rochelle DG. Response of the transplanted denervated human heart to cardiovascular drugs. *American Journal of Cardiology* 1971; 27: 272-276.
- McGriffin DC, Bonker JR, Kirklin JK, Naftel DC. Patterns of infection and management in cardiac transplantation. In: Wallwork J, ed. *Heart and Lung Transplantation*. Philadelphia: W. B. Saunders, 1989; 251-298.
- MacLeod A, Catto GRD. Cancer after transplantation. *British Medical Journal* 1988; 297: 4-5.
- Mason JW, Stinson EB, Harrison DC. Autonomic nervous system and arrhythmias: Studies in the transplanted denervated human heart. *Cardiology* 1976; 61: 75-87.
- Penn I. Tumour incidence in human allograft recipients. *Transplant Proceedings* 1979; 9: 1047-1051.
- Ream AK, Fowles RE, Jamieson S. Cardiac transplantation. In: Kaplan JA, ed. *Cardiac Anaesthesia*. Orlando: Grune and Stratton, 1987; 881-891.
- Sale JP, Patel D, Duncan B, Water JH. Anaesthesia for combined heart and lung transplantation. *Anaesthesia* 1987; 42: 249-258.
- Samuels SI, Kanter SF. Anaesthesia for major surgery in a patient with a transplanted heart. *British Journal of Anaesthesia* 1977; 49: 265-267.
- Schroeder JS, Berke DK, Graham AF, Rider AK, Harrison DC. Arrhythmias after cardiac transplantation. *American Journal of Cardiology* 1974; 33: 604-607.
- Steed DL, Brown B, Reilly JJ, Pietzman AB, Griffith BP, Hardesty RL, Webster MW. General surgical complications in heart and heart-lung transplantation. *Surgery* 1985; 98: 739-744.
- Theodore J, Jamieson SW, Burke CM, Reitz BA, Stinson EB, Van Kessel AV, Dawkins KD, Herran JJ, Oyer PE, Hunt SA, Shumway NE, Robin ED. Physiological aspects of human heart-lung transplantation. Pulmonary function status of the post transplanted lung. *Chest* 1984; 86: 349-357.
- Veith FJ, Kamholz L, Mollenkopf P, Montefusco CM. Lung transplantation 1983. *Transplantation* 1983; 35: 271-277.

P6 ACUPUNCTURE AND POSTOPERATIVE VOMITING AFTER TONSILLECTOMY IN CHILDREN

S. M. YENTIS AND B. BISSONNETTE

SUMMARY

We have studied the effect of P6 acupuncture on postoperative vomiting in 45 children undergoing tonsillectomy. After induction of anaesthesia and before the start of surgery, 50% of the patients received P6 acupuncture (in the middle of the ventral surface of the wrist) for 5 min. There was no difference in the incidence of vomiting between the acupuncture (39%) and non-acupuncture (36%) groups. We conclude that, when administered after induction of anaesthesia, P6 acupuncture is ineffective in reducing vomiting after tonsillectomy in children.

KEY WORDS

Anaesthesia: paediatric. Anaesthetic techniques: acupuncture. Surgery: tonsillectomy, paediatric. Vomiting: incidence.

Vomiting is common after paediatric tonsillectomy, with a reported incidence of up to 81% [1]. Stimulation of the P6 acupuncture point has been shown to reduce nausea and vomiting significantly in adults undergoing gynaecological procedures [2, 3] and chemotherapy [4], and has no side effects [2]. This point ("Neiguan") is situated two "Chinese inches" (two widths of the interphalangeal joint of the patient's thumb) proximal to the distal skin crease of the wrist [2]. Children often respond well to acupuncture in general, and are included in the group termed "strong reactors" [5]. P6 acupuncture and postoperative vomiting has not been studied previously in children.

The purpose of this study was to evaluate the antiemetic effect of P6 acupuncture in children undergoing tonsillectomy. Although acupuncture is painless and tolerated well by adults, we felt that most children would be too scared to accept it when awake; consequently the acupuncture was administered after induction of anaesthesia.

METHODS AND RESULTS

After approval by the Human Subjects Review Committee, we obtained informed written consent from the parents of 45 children of ASA physical status I or II presenting for elective tonsillectomy. The children were allocated randomly to two groups, the sizes being determined by power analysis assuming a value for α of 0.05, β of 0.2, control incidence of vomiting of 80% and post-acupuncture incidence of 40%. No premedication was given. Anaesthesia was induced with i.v. thiopentone 5 mg kg⁻¹, atropine 0.02 mg kg⁻¹, and suxamethonium 1.5 mg kg⁻¹. Manual inflation of the lungs (taking care not to inflate the stomach) was followed by tracheal intubation and spontaneous ventilation with 66% nitrous oxide and 1.5-2.0% isoflurane in oxygen. The children in one group received acupuncture at the P6 point on the left side with 5 min manual stimulation, using sterile, disposable 0.2-mm diameter acupuncture needles. The acupuncture was administered by one investigator (S.Y.) immediately after tracheal intubation and before the start of surgery.

I.m. codeine 1.5 mg kg⁻¹ was administered to all patients at the end of surgery. Estimated fluid deficit and maintenance requirements were replaced with i.v. Ringer's lactate solution. After operation, i.m. dimenhydrinate 1.0 mg kg⁻¹ was available if the incidence of vomiting exceeded three episodes during any 1-h period. Further i.m. codeine 1.0 mg kg⁻¹ or oral paracetamol 10 mg kg⁻¹ was available on the ward as required for pain.

The incidence of vomiting, retching or both

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TABLE I. Patient data (mean (SD or range)) and incidence of vomiting following tonsillectomy (No. (%))

	Control (n = 22)	Acupuncture (n = 23)
Age (yr)	6.7 (2-11)	5.7 (2-10)
Duration of anaesthesia (min)	24 (7)	26 (7)
Time to first drink (min)	96.0 (53.7)	75.5 (27.1)
Time to discharge (h)	19.8 (1.5)	19.4 (1.4)
Postoperative vomiting	8 (36%)	9 (39%)

was recorded in the postanesthetic recovery room (PAR) and ward. Staff, patients and parents were unaware of whether or not acupuncture was given. Other data collected included age, sex, duration of anaesthesia, duration of stay in the PAR, postoperative drug requirements, time to drinking fluids and time to discharge from hospital.

Statistical significance ($P < 0.05$) was determined using the unpaired t test for age, duration of anaesthesia, duration of stay in the PAR and time to drinking and discharge from hospital; chi-square analysis was used for sex distribution, postoperative drug requirements and incidence of vomiting.

There was no significant difference between the groups for any of the variables recorded. The incidence of vomiting was 39% and 36%, with and without acupuncture, respectively (table I). All but one patient in each group underwent adenoidectomy in addition to tonsillectomy.

COMMENT

We were unable to demonstrate any antiemetic effect of P6 acupuncture in children undergoing tonsillectomy. There are several possible reasons for this.

First, P6 acupuncture might be ineffective in children, although their description as "strong reactors" would suggest otherwise [5]. Second, it may be ineffective for tonsillectomy; vomiting after tonsillectomy is likely to be multifactorial, related to pharyngeal stimulation, psychological factors, swallowing of blood and administration of opioid drugs. Third, a longer period of time might be required between the acupuncture and surgery, as better results have been achieved when acupuncture was performed 1 h before operation than immediately before induction [2].

It has been suggested that P6 acupuncture is

effective only when administered before the emetic stimulus [4]. However, Ho and colleagues found a significant reduction in postoperative vomiting when electroacupuncture was administered in the recovery room [3]. In another study, no antiemetic effect was demonstrated for acupuncture administered during general anaesthesia [6]. It is thus possible that general anaesthesia is the most important factor in reducing any antiemetic effect of acupuncture. This may be caused partly by a greater incidence of incorrect or inadequate needling, as the patients would be anaesthetized and thus unable to describe the sensation of heaviness or dullness ("Chi") that often accompanies correct placement [2, 3]. In addition, administration during anaesthesia would eliminate psychological factors, although "dummy" acupuncture has no antiemetic effect, suggesting that psychological factors are not important [2]. The effect of general anaesthesia on that of acupuncture is unclear, although anaesthesia is more likely to depress than to enhance it [3].

In conclusion, P6 acupuncture administered after induction of anaesthesia is ineffective in reducing postoperative vomiting following paediatric tonsillectomy. Further studies are needed to determine the place of acupuncture in paediatric anaesthesia. However, we suspect that administration to the awake paediatric patient may prove unacceptable, especially to younger children and their parents.

REFERENCES

1. Van der Walt JH, Jacob R, Murrell D, Bentley M. The perioperative effect of oral premedication in children. *Anaesthesia and Intensive Care* 1990; 18: 5-10.
2. Dundee JW, Ghaly RG, Bill KM, Chestnutt WN, Fitzpatrick KTJ, Lynas AGA. Effect of stimulation of the P6 antiemetic point on postoperative nausea and vomiting. *British Journal of Anaesthesia* 1989; 63: 612-618.
3. Ho RT, Javan B, Fung ST, Cheung HK, Lee JH. Electro-acupuncture and postoperative emesis. *Anaesthesia* 1990; 45: 327-329.
4. Dundee JW, Ghaly RG, Fitzpatrick KTJ, Abram WP, Lynch GA. Acupuncture prophylaxis of cancer chemotherapy-induced sickness. *Journal of the Royal Society of Medicine* 1988; 82: 268-271.
5. Mann F. *Scientific Aspects of Acupuncture*, 2nd Edn. London: Heinemann, 1981.
6. Weightman WM, Zacharias M, Herbison P. Traditional Chinese acupuncture as an antiemetic. *British Medical Journal* 1987; 295: 1379-1380.

DOSE REQUIREMENTS OF ATRACURIUM IN PAEDIATRIC INTENSIVE CARE PATIENTS

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AND G. MEAKIN

SUMMARY

The dose requirements of atracurium were determined in 12 children who required an infusion of atracurium to facilitate mechanical ventilation in the intensive care unit. The mean duration of infusion was 98 h (range 36-284 h) during which an increasing dose requirement was observed in all patients. The mean infusion rate was 1.60 (SEM 0.08) mg kg⁻¹ h⁻¹, and in seven patients a mean infusion rate of 1.72 (0.15) mg kg⁻¹ h⁻¹ was observed at 72 h. These rates are greater than those reported previously in adults. Cessation of neuromuscular block occurred promptly upon discontinuing the infusion. No side effects were observed which could be attributed to the infusion of atracurium.

KEY WORDS

Intensive care: paediatric. Neuromuscular relaxants: atracurium.

Prolonged infusions of atracurium are used widely to facilitate mechanical ventilation in the intensive care unit (ICU). In adults, Yate and co-workers found an increasing dose requirement within the first 72 h of starting an atracurium infusion [1]. This study was designed to determine if a similar effect occurs in children.

METHODS AND RESULTS

After obtaining Ethics Committee approval, we studied 12 children with a mean age of 8 yr (range 2-15 yr) and mean weight 22.6 kg (range 8.6-40.2 kg) who required administration of atracurium to facilitate mechanical ventilation in the ICU. Atracurium was the only neuromuscular blocking agent used in the study and none of the

patients was grossly under- or overhydrated. Background sedation was provided by i.v. infusion of midazolam 0.1-0.2 mg kg⁻¹ h⁻¹, supplemented with bolus doses of fentanyl 1-2 µg kg⁻¹ h⁻¹ as necessary.

An infusion of undiluted atracurium 10 mg ml⁻¹ was delivered into a central or peripheral vein from a 50-ml syringe via a Treonic IP3 infusion pump (Vickers Medical). The infusion was connected to the i.v. cannula or catheter via a 15-cm extension set with a three-way stopcock having a total capacity of 0.5 ml (Viggo-Spectramed). The atracurium infusion was commenced at a rate of 0.5 mg kg⁻¹ h⁻¹ and adjusted by the nursing staff of the ICU to provide good conditions for mechanical ventilation. In order to prevent gross overdosage with atracurium, neuromuscular transmission was assessed at least every 8 h using a peripheral nerve stimulator (Bard 750 Digital). The assessment comprised tactile inspection of the response of the adductor muscles of the thumb to train-of-four (TOF) stimulation of the ulnar nerve. The infusion was increased at the first sign of patient movement, but decreased if there was no response to TOF stimulation. Rates of infusion were recorded by the nursing staff on a specially designed chart. When the infusion was discontinued, time to full recovery of neuromuscular function (four equal twitches to TOF stimulation) was noted. Results were expressed as mean (SEM). The statistical significance of the relationship between mean infusion rate and the

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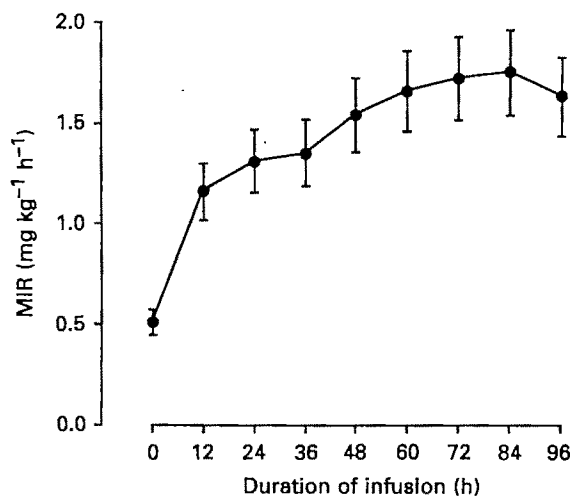


FIG. 1. Mean (SEM) infusion rates (MIR) of atracurium at various times after commencing an infusion.

duration of infusion was determined by repeated measures analysis of variance. Significant differences between means were determined using Student's *t* test. The null hypothesis was rejected when $P < 0.05$.

The mean duration of infusion was 98 h (range 36–284 h), during which an increased dose requirement was observed in all patients ($P < 0.001$) (fig. 1). The average infusion rate was 1.60 (0.08) $\text{mg kg}^{-1} \text{h}^{-1}$ and in seven patients a mean infusion rate of 1.72 (0.15) $\text{mg kg}^{-1} \text{h}^{-1}$ was observed at 72 h. There was no significant correlation between the infusion rate and age, body temperature or blood pH.

An investigator was available to record recovery details in seven patients. The mean time from the end of the infusion to full recovery of neuromuscular transmission was 23.7 (3.1) min (range 10–35 min). There were no deaths in the course of the study. No patient required antagonism of neuromuscular block and no side effects which could be attributed to atracurium were observed.

COMMENT

The finding of an increase in the dose of atracurium required by children during the first 72 h of an infusion agrees with earlier work in adults [1]. However, both the mean infusion rate for the study and the rate at 72 h were greater than those reported previously in adults (0.76 (0.05) $\text{mg kg}^{-1} \text{h}^{-1}$ and 0.76 (0.06) $\text{mg kg}^{-1} \text{h}^{-1}$ respectively ($P < 0.001$)) [1].

The cause of the resistance to atracurium when given by prolonged infusion has been investigated in dogs by Chappel and colleagues [2]. These authors showed that prolonged immobilization produced by pentobarbitone anaesthesia resulted in a similar degree of resistance to atracurium as that produced by infusion of the drug itself. Hence, they concluded that immobility, rather than neuromuscular block, was the cause of the resistance. A similar effect has been reported after prolonged infusion of pancuronium [3].

Prolonged immobilization may produce resistance to neuromuscular blocking drugs by allowing acetylcholine receptors to spread beyond the neuromuscular junction [4]. This appears to be a reversal of the normal developmental sequence, in which muscle activity is thought to be an important factor in reducing the number of extrajunctional receptors [5]. These extrajunctional receptors have binding properties for neuromuscular blocking drugs which differ little from those of junctional receptors. Thus, following prolonged immobilization, it is likely that a significant proportion of a dose of a non-depolarizing neuromuscular blocking drug is bound at extrajunctional sites.

The much greater infusion rates required by children in the present study compared with adults may be explained by differences in pharmacokinetics and clinical methods. At a steady state, the amount of drug administered is equal to that eliminated, the product of clearance and the steady state plasma concentration. As the clearance of atracurium is 28% greater in children than in adults [6] this would be expected to result in greater rates of infusion. The greater infusion rates in children may also have resulted from the fact that they apparently required a greater degree of neuromuscular block to facilitate mechanical ventilation. Our patients usually required at least 90% depression of the twitch response, while a typical adult required about 60% [1]. This difference would be expected to increase the infusion requirements of the children by approximately 75% [6].

Concern has been expressed about the possible toxic effects of laudanosine, a metabolite of atracurium which has a longer half-life than the parent compound, and which may therefore accumulate during prolonged atracurium administration. In dogs, small blood concentrations have been shown to produce awakening, while greater concentrations ($17 \mu\text{g kg}^{-1}$) caused con-

vulsions [7]. While these effects were not observed in our patients, they could have been masked by either sedation or neuromuscular block. In view of the greater dose requirements of atracurium in paediatric intensive care patients compared with adults, further investigation would appear to be indicated to determine the plasma concentrations of laudanosine in these patients.

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REFERENCES

1. Yate PM, Flynn PJ, Arnold RW, Weatherly BC, Simmonds RJ, Dopson T. Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. *British Journal of Anaesthesia* 1987; 59: 211-217.
2. Chapple DJ, Dodd P, Macleod DM, Withington PS, Yate PM. Requirements for neuromuscular blocking agents during prolonged anaesthesia in the anaesthetized dog. *British Journal of Anaesthesia* 1987; 59: 1321P-1322P.
3. Gronert GA. Disuse atrophy with resistance to pancuronium. *Anesthesiology* 1981; 55: 547-549.
4. Fambrough DM. Control of acetylcholine receptors in skeletal muscle. *Physiological Reviews* 1979; 59: 165-227.
5. Schuetz SM, Role LW. Developmental regulation of nicotinic acetylcholine receptors. *Annual Review of Neurosciences* 1987; 10: 403-457.
6. Fisher DM, Canfell PC, Spellman MJ, Miller RD. Pharmacokinetics and pharmacodynamics of atracurium in infants and children. *Anesthesiology* 1990; 73: 33-37.
7. Hennis PJ, Fahey MR, Canfell PC, Shi W-Z, Miller RD. Pharmacology of laudanosine in dogs. *Anesthesiology* 1986; 65: 56-60.

MANAGEMENT OF LABOUR AND DELIVERY IN PATIENTS WITH INTRACRANIAL NEOPLASMS

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SUMMARY

The presence of an intracranial neoplasm (ICN) during pregnancy has serious implications for the anaesthetic management of labour and delivery. The physiological changes of pregnancy and labour are potentially hazardous to women with ICN, but the provision of adequate pain relief during labour reduces the risk to the mother. Extradural anaesthesia is the only technique that provides pain-free labour reliably, but it carries added risks. Three patients are reported who were managed with extradural anaesthesia: two delivered per vaginam and one by Caesarean section. None suffered any complication related to the anaesthetic technique. At present, there are no published data on the influence of anaesthetic management on outcome of labour and delivery in patients with ICN. Anaesthetists should report such cases so that the relative risks of different management strategies may be assessed.

KEY WORDS

Anaesthesia: obstetric. Pregnancy: complications, intracranial neoplasm.

CASE REPORTS

Patient No. 1

A 31-yr-old nulliparous woman was admitted to the delivery suite at 27 weeks gestation with painful regular contractions. A malignant melanoma had been removed from her back 18 months previously. Investigation revealed the presence of secondary deposits in the liver and lungs. On the third day of her admission she suffered a grand mal seizure; CT-scan showed the presence of multiple intracranial deposits, with surrounding oedema. She was treated with cranial irradiation, dexamethasone and carbamazepine and was left

with a mild hemiparesis but suffered no further seizures. At 29 weeks gestation she went into spontaneous labour. It had been decided that delivery should be by Caesarean section and the patient requested extradural anaesthesia. At this time, she had no symptoms or signs suggestive of increased intracranial pressure (ICP). An extradural catheter was inserted via the L3-4 interspace and anaesthesia was produced with 15 ml of 2% lignocaine with 1:200 000 adrenaline. Systolic arterial pressure was maintained at 100-120 mm Hg with i.v. fluids and ephedrine. The patient was delivered of a live, healthy male infant. Immediate postoperative recovery was uneventful, but her condition deteriorated over the next few days and she died on the ninth day after operation.

Patient No. 2

A 28-yr-old nulliparous woman was admitted to the delivery suite for induction of labour. She was known to have a prolactin-secreting pituitary macroadenoma.

Pregnancy had been complicated by headaches and symptoms of optic nerve compression which had responded to treatment with bromocriptine. The recurrence of headache led to her admission for induction of labour. At the instigation of her neurosurgeon, and after discussion with her obstetrician, it was decided that extradural analgesia was indicated to reduce the risk of haemorrhage from the tumour during labour. She did not have symptoms or signs of increased ICP and her headaches were attributed to tumour expansion. An extradural catheter was introduced

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via the L2–3 interspace and analgesia was produced with 0.25 % plain bupivacaine 15 ml. After a single top-up of 0.5 % plain bupivacaine 15 ml, she was delivered of a live female infant by forceps. The puerperium was uneventful. A CT-scan showed the tumour to have enlarged during pregnancy. Treatment with bromocriptine was continued whilst she awaited surgical removal of the tumour.

Patient No. 3

A search of the hospital records revealed another patient with an ICN who had delivered in the preceding 6 months. She was a 41-yr-old multiparous woman who went into labour at 33 weeks gestation. She was managed with extradural analgesia and delivered spontaneously *per vaginam*. Two days later, she complained of blurred vision and CT-scan showed a sphenoidal ridge meningioma, the presence of which was unknown at the time of insertion of the extradural catheter.

DISCUSSION

The prevalence of ICN in pregnancy is not known. A survey of the incidence of ICN in the U.S.A. estimated the incidence in women of child-bearing age as 3.4 per 100 000 in the 15–24 yr age group, increasing to 13.2 per 100 000 in the 35–44 yr age group [1]. The age-adjusted rates were greater for men than for women, but meningiomas and pituitary adenomas were commoner in women than in men.

Few studies of the incidence of ICN in pregnancy have been published. In East Germany, ICN were the sixth most common tumour diagnosed in pregnancy [2] and the incidence of newly diagnosed primary malignant ICN in pregnant women was 3.6 per million live births [3]. A recent review of pregnancy-related primary brain and spinal tumours [4] concluded that the relative frequency of the different types of primary brain tumours is not altered by pregnancy, but that the incidence of brain tumours that become symptomatic during pregnancy was lower than that in age-matched non-pregnant women. The most recent report into maternal deaths in England and Wales [5] included six deaths caused by ICN.

During pregnancy and labour, profound physiological changes occur, some of which pose a significant threat to the patient with an ICN. Of the six deaths caused by ICN and reported in the

most recent report into maternal deaths in England and Wales, one death was classed as an indirect death—that is, “a death resulting from a pre-existing disease which is not due to direct obstetric causes but which is aggravated by the physiologic effects of pregnancy”. Despite the many case reports and reviews regarding ICN in pregnancy, the literature discussing the anaesthetic management is limited to two brief case reports [6, 7]. As a result, anaesthetists faced with this problem have to base their management on theoretical knowledge of obstetric and neuro-surgical anaesthesia and of the effects of the physiological changes of pregnancy and labour on the cerebral circulation, ICP and the tumour.

During pregnancy, blood volume increases by about 35 %, cardiac output increases by 40–50 % and plasma osmolality and albumin concentrations decrease. These changes, combined with salt and water retention, may predispose to the formation of cerebral oedema. The constituents and pressure of cerebrospinal fluid are unaltered during normal pregnancy [8]. The symptoms of an ICN may worsen during pregnancy and improve during the puerperium [9–12]. In some women, the symptoms also worsen during the premenstrual week [11], supporting the hypothesis that fluid retention during pregnancy causes expansion of ICN and local oedema formation. One review of women with untreated pituitary tumours found that 60 % remained asymptomatic throughout pregnancy, whilst 30 % required treatment for symptoms of tumour expansion [13]. In the case of pituitary tumours, the expansion may result from both fluid retention and the pituitary cellular hypertrophy that occurs during pregnancy [14]. Despite the worsening of symptoms that may accompany pregnancy, the overall outcome is generally good. However, patients with malignant or infra-tentorial tumours are more likely to suffer serious morbidity as a result of the pregnancy [12].

During labour, ventilatory frequencies of up to 70 b.p.m. and tidal volumes of up to 2.25 litre have been recorded [15]. Minute ventilation may reach 90 litre min^{-1} . Arterial partial pressure of carbon dioxide decreases progressively to an average of 3.3 kPa, and may be as little as 2.1 kPa during contractions [16]. In patients with an ICN, this may result theoretically in an inverse steal effect, with local oedema formation. Cardiac output increases during labour and may be as great as 10 litre min^{-1} ; with each contraction,

systolic arterial pressure increases by 20–30 mm Hg and diastolic by 15–20 mm Hg [17, 18]. These fluctuations in arterial pressure may result in acute changes in cerebral blood flow (CBF) and ICP. During the first stage of labour, CSF pressure increases by up to 39 cm H₂O with each contraction and during the second stage, bearing down causes an average increase in CSF pressure of 71 cm H₂O [19]. Patients with an ICN may have reduced cerebral compliance and may suffer even greater increases in ICP.

The acute physiological changes of labour summarized above are greatly diminished if labour is pain free. Hyperventilation and hypocarbia are abolished and maternal oxygenation improves [20–22]. The increase in cardiac output that occurs during labour, and the increase in arterial pressure that accompanies contractions are reduced by about 50 % [22]. Abolition of hyperventilation and the bearing down reflex prevents the increase in CSF pressure that accompanies painful contractions. [19].

Whether delivery is by Caesarean section or *per vaginam* is largely a decision for the obstetrician in charge of the patient's care. However, anaesthetic management should be a factor in this decision. If delivery is to be *per vaginam*, the provision of pain free labour minimizes the acute physiological disturbances and reduces the risk of cerebral oedema formation and of intracranial haemorrhage. Opioids and nitrous oxide should be avoided, as neither consistently provides pain free labour and both may increase CBF and cause patient disorientation. Extradural block is the only applicable technique that consistently provides pain free labour, but its use in patients with ICN carries additional risks. Hypotension occurs in up to 6 % of patients [23] and in order to maintain cerebral perfusion pressure this must be treated aggressively. In the presence of increased ICP, or reduced cerebral compliance, extradural injection may result in an increase in ICP [24]. The degree and duration of the increase is related to the volume of the injectate and the use of a very slow rate of injection has been recommended [25]. Women with active epilepsy may have an increased incidence of convulsions during labour if they receive extradural analgesia [26] and use of the technique in a patient with an ICN who has suffered a convulsion may carry the same increased risk.

The most serious concern is the risk of dural puncture, as this may lead to acute neurological

deterioration [27]. Symptoms and signs of increased ICP must be sought actively, but their absence does not exclude the presence of increased ICP [27]. The risk of dural puncture depends on the experience of the operator, but in experienced hands it may be as low as 0.2 % [28]. The risk of dural puncture is reduced by using the sacral approach, but is not abolished; however, caudal anaesthesia provides inadequate analgesia in 10–20 % of subjects, whereas in experienced hands the lumbar approach provides adequate analgesia in 98 % [26]. Caudal anaesthesia also requires larger doses of local anaesthetic, which results in greater risk of maternal toxicity [29].

In some patients, management may be complicated further by the need for definitive treatment of the tumour. If surgery is planned in late pregnancy, the option of combining the neurosurgical procedure with an elective Caesarean section may make general anaesthesia the anaesthetic technique of choice. There are many reports of neurosurgical procedures during pregnancy, both for ICN and for subarachnoid haemorrhage [30, 31]. Standard neurosurgical anaesthetic techniques including induced hypotension [32] have been used without adverse effect on the fetus.

The management of labour and delivery in a patient with an ICN is a complex problem. None of the management options is without risk and at present there are insufficient data in the literature to guide decision making. Patients should be assessed carefully and the symptoms and signs of increased ICP sought actively. Patients with a small tumour and no signs of increased ICP may reasonably be allowed to labour. Analgesia by lumbar extradural block has many advantages and should be considered. Whether these advantages justify the risk of dural puncture has to be judged in each individual patient. Bearing down and pushing should be avoided; a short second stage with forceps delivery is desirable. Failure to achieve adequate analgesia, or a deterioration in the patient's neurological condition, may be considered indications to proceed to Caesarean section under general anaesthesia. In patients with a large tumour, signs of increased ICP or focal neurological signs, the balance of risks may favour elective Caesarean section under "neurosurgical" general anaesthesia. Until the anaesthetic management of such patients has been reported in greater numbers, the balance of risks remains a matter of conjecture.

REFERENCES

- Walker AE, Robins M, Weinfeld FD. Epidemiology of brain tumours: The national survey of intracranial neoplasms. *Neurology* 1985; 35: 219-226.
- Haas JF. Pregnancy in association with a newly diagnosed cancer: A population-based epidemiologic assessment. *International Journal of Cancer* 1984; 34: 229-235.
- Haas JF, Janisch W, Staneczek W. Newly diagnosed primary intracranial neoplasms in pregnant women: A population-based assessment. *Journal of Neurology, Neurosurgery and Psychiatry* 1986; 49: 874-880.
- Roelvink NCA, Kamphorst W, van Alphen HAM, Rao BR. Pregnancy-related primary brain and spinal tumors. *Archives of Neurology* 1987; 44: 209-215.
- Turnbull A, Tindall VR, Beard RW, Robson G, Dawson IMP, Cloake EP, Ashley JSA, Botting B. *Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1982-1984*. London: Her Majesty's Stationary Office, 1989.
- Kepes ER, Andrews IC, Radnay PA, Schapira M, Stark DCC. Conduct for anesthesia for delivery with grossly raised cerebrospinal fluid pressure. *New York State Journal of Medicine* 1972; 72: 1155-1156.
- Goroszeniuk T, Howard RS, Wright JT. The management of labour using continuous lumbar epidural analgesia in a patient with a malignant cerebral tumour. *Anaesthesia* 1986; 41: 1128-1129.
- Marx GF, Orkin LR. Cerebrospinal fluid proteins and spinal anesthesia in obstetrics. *Anesthesiology* 1965; 26: 340-343.
- O'Connell JEA. Neurosurgical problems in pregnancy. *Proceedings of the Royal Society of Medicine* 1962; 55: 577-582.
- Michelson JJ, New PFJ. Brain tumour and pregnancy. *Journal of Neurology, Neurosurgery and Psychiatry* 1969; 32: 305-307.
- Bickerstaff ER, Small JM, Guest IA. The relapsing course of certain meningiomas in relation to pregnancy and menstruation. *Journal of Neurology, Neurosurgery and Psychiatry* 1958; 21: 89-91.
- Kempers RD, Miller RH. Management of pregnancy associated with brain tumours. *American Journal of Obstetrics and Gynecology* 1963; 87: 858-864.
- Magyar DM, Marshall JR. Pituitary tumors in pregnancy. *American Journal of Obstetrics and Gynecology* 1978; 132: 739-751.
- Goluboff LG, Erzin C. Effect of pregnancy on the somatotroph and prolactin cells of the human adenohypophysis. *Journal of Clinical Endocrinology and Metabolism* 1969; 29: 1533-1538.
- Cole PV, Nainby-Luxmore RC. Respiratory volumes in labour. *British Medical Journal* 1962; 1: 1118.
- Anderson GJ, Walker J. The effect of labour on the maternal blood-gas and acid-base status. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1970; 77: 289-293.
- Ueland K, Hansen JM. Maternal cardiovascular dynamics. II. Posture and uterine contractions. *American Journal of Obstetrics and Gynecology* 1969; 103: 1-7.
- Hendricks CH, Quilligan BJ. Cardiac output during labour. *American Journal of Obstetrics and Gynecology* 1956; 71: 953-972.
- Marx GF, Zamaitis MT, Orkin LR. Cerebrospinal fluid pressures during labor and obstetrical anesthesia. *Anesthesiology* 1961; 22: 348-354.
- Fisher A, Prys-Roberts C. Maternal pulmonary gas exchange. A study during normal labour and extradural blockade. *Anaesthesia* 1968; 23: 350-356.
- Pearson JF, Davies P. The effect of continuous lumbar epidural analgesia on the acid-base status of maternal arterial blood during the first stage of labour. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1973; 80: 218-224.
- Bonica JJ. Pain of parturition. *Clinics in Anesthesiology* 1986; 4: 1-31.
- Moore J, Murnaghan GA, Lewis MA. A clinical evaluation of the maternal effects of lumbar extradural analgesia for labour. *Anaesthesia* 1974; 29: 537-544.
- Hilt H, Gramm H-J, Link J. Changes in intracranial pressure associated with extradural anaesthesia. *British Journal of Anaesthesia* 1986; 58: 676-680.
- Wildsmith JAW. Extradural blockade and intracranial pressure. *British Journal of Anaesthesia* 1986; 58: 579.
- Anderson S. Management of epilepsy. *Lancet* 1990; 336: 1127.
- Richards PG, Towu-Aghantse E. Dangers of lumbar puncture. *British Medical Journal* 1986; 292: 605-606.
- Moir DD, Thorburn J. *Obstetric Anaesthesia and Analgesia*, 3rd Edn. London: Baillière Tindall, 1986.
- Russell PH, Coakley CS. Re-evaluation of continuous caudal anesthesia for obstetrics. *Surgery, Gynecology and Obstetrics* 1964; 119: 531-534.
- Falconer MA, Stafford-Bell MA. Visual failure for pituitary and parasellar tumours occurring with favourable outcome in pregnant women. *Journal of Neurology, Neurosurgery and Psychiatry* 1975; 38: 919-930.
- Minielly R, Yuzpe AA, Drake CG. Subarachnoid haemorrhage secondary to ruptured cerebral aneurysm in pregnancy. *Obstetrics and Gynecology* 1979; 53: 64-70.
- Donchin Y, Amirav B, Sahar A, Yarkoni S. Sodium nitroprusside for aneurysm surgery in pregnancy. *British Journal of Anaesthesia* 1978; 50: 849-851.



NON-INVASIVE MEASUREMENT OF CARDIAC OUTPUT BY THORACIC ELECTRICAL BIOIMPEDANCE: A STUDY OF REPRODUCIBILITY AND COMPARISON WITH THERMODILUTION

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SUMMARY

The performance and reproducibility of the BoMED NCCOM3 thoracic electrical bioimpedance cardiograph (TEB) has been evaluated in volunteers and patients. In resting supine volunteers, we determined the coefficient of variability over short time periods (30 min) and over several days, and examined the effects of differences in electrode type and electrode placement. The mean (range) intra-subject coefficients of variation (CV) for thoracic fluid index (TFI) and stroke volume (SV) were 1.0% (0.4-1.8%) and 4.7% (2.1-8.5%), respectively over a 30-min period. The corresponding CV were 5.6% (2.3-10.9%) and 10.9% (6.1-14.8%) for measurements made at rest on four separate occasions. Use of different electrode types (RedDot and Medicotest) resulted in differences in TFI ($P < 0.01$), but not in mean values for SV or cardiac output ($\dot{Q}$); their use in individual subjects revealed differences of up to 20% in SV and $\dot{Q}$. Alterations in electrode placement by 5 cm in the horizontal and diagonal planes produced no significant changes in TFI, SV or $\dot{Q}$; changes in the longitudinal plane produced a graded change. Increases of 5 cm and 10 cm in thoracic length produced mean increases in TFI of 9.8% and 39.8%, respectively, and mean decreases in $\dot{Q}$ of 8.4% and 16.7% and SV of 7.5% and 15.8%. TEB measurements of $\dot{Q}$ and SV were compared with thermodilution (TD) in 16 intensive care patients. Mean (SEM) $\dot{Q}$ by TEB was 5.63 (1.10) litre min^{-1} compared with TD 4.38 (0.72) litre min^{-1} ($P < 0.01$). The correlation coefficient for $\dot{Q}$ (r) was 0.72, producing the equation $\dot{Q}_{\text{TEB}} = 0.835 \times \dot{Q}_{\text{TD}} + 1.13$; that for SV was $r = 0.83$, $\text{SV}_{\text{TEB}} = 1.009 \times \text{SV}_{\text{TD}} + 6.84$. Bias

between the two methods revealed a mean difference of -0.86 litre min^{-1} (95% confidence limits -2.6 to $+0.89$) for $\dot{Q}$, and -13 ml (-35.2 to $+9.2$) for SV. Analysis of individual patient bias plots revealed two different trends. If the range of $\dot{Q}$ values was < 1.0 litre min^{-1} , there was a variable bias of magnitude similar to that seen in the volunteer studies. If values of $\dot{Q}$ had a range of > 1.0 litre min^{-1} , there tended towards a constant bias for that individual patient, indicating that TEB is able to follow trends.

KEY WORDS

Measurement techniques: cardiac output, thoracic electrical bioimpedance.

The technique of thoracic electrical bioimpedance (TEB) was introduced into clinical practice by Kubicek and colleagues [1] in 1966. Since then, several studies have reported comparisons of the method with various other techniques for measuring cardiac output ($\dot{Q}$) [2-8]. These studies have reported different correlation coefficients, varying from good ($r = 0.97$ [4]), to poor ($r = 0.41$ [8]). The original Kubicek formula for stroke volume (SV) was:

$$\text{SV} = p(L^2/Z_0^2) \cdot (dZ/dr)_{\text{max}} \cdot \text{LVET}$$

where p = resistivity of blood; L = distance between the inner two electrodes; Z_0 = mean basal

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thoracic impedance; dZ/dt = first derivative of impedance; LVET = left ventricular ejection time.

A new impedance cardiograph, the BoMED NCCOM3 (Irvine, CA) has improved on several disadvantages of the original Minnesota Impedance Cardiograph. It has replaced the band electrodes with pairs of standard ECG electrodes, which improves patient acceptance. It also has an integrated computer using a new algorithm based on the Bernstein-Sramek formula [9] which allows on-line calculation of SV and $\dot{Q}$. There have been several studies comparing the NCCOM3 with thermodilution (TD) [8, 10-13] and these have shown reasonable correlation coefficients. However, apart from incidental reports, there has been no evaluation of the variability and reproducibility of the NCCOM3, or study of the effects of different electrode types and positions.

PATIENTS AND METHODS

Variability

This phase of the evaluation comprised four parts. In each part, normal volunteers were studied in the supine position at rest and recordings made after a 20-min stabilization period. The BoMED NCCOM3 was used to measure cardiac output, stroke volume, heart rate (HR), and basal impedance (Z_0) or thoracic fluid index (TFI).

Two "sensing" electrode pairs were placed on the thorax at the level of the xiphisternum in the mid-axillary line and on the lateral aspect of the neck immediately above the clavicles. The other two pairs of the "current injecting" electrodes were placed 5 cm above the cervical and below the thoracic sensing electrodes. The current injecting electrodes deliver a 2.5-mA, 70-kHz, alternating current. The NCCOM3 calculates SV from the Bernstein-Sramek formula [9]:

$$SV = VEPT \times VET \times (dZ/dt_{max})/Z_0$$

where VEPT is volume of electrically participating tissue (calculated as $d[(0.17H)^3]/4.25$, where d is a scaling factor proportional to the ratio observed:ideal weight, H = height in cm), VET is the ventricular ejection time, dZ/dt_{max} is the rate of change of impedance during systole, and Z_0 (or TFI) is the basal thoracic impedance. The NCCOM3 was set to average 16 beats and all digital output were recorded on a Thinkjet Printer

(Hewlett-Packard). The analogue output from the NCCOM3 was recorded also on a chart recorder, to permit examination of the dZ/dt waveform.

In the first group of subjects, the electrodes were placed in the position recommended by the manufacturer and a non-invasive arterial pressure cuff was applied to the upper arm. After the 20-min stabilization period, recordings were made of TFI, SV, $\dot{Q}$, HR and systolic, diastolic and mean arterial pressures (Dinamap 845XT, Critikon) every 5 min for 30 min. For TEB data, three readings were averaged over the time taken to record the arterial pressure. Reproducibility for each subject was calculated as the coefficient of variability for each cardiovascular variable.

In the second group of subjects, variability was studied over several days. The electrodes were placed in the manufacturer recommended positions, and after a 20-min stabilization period TFI, SV, $\dot{Q}$ and HR were recorded for 10 readings. The subjects repeated this procedure on four occasions with an interval between tests of at least 12 h.

In a third group of subjects, the effect of different electrode types was studied. The initial electrodes were Medicotest (Olstaggke, Denmark), which were replaced by RedDot (3M, Canada) and TFI, SV, $\dot{Q}$ and HR re-recorded. Ten readings for each variable and for each electrode type were averaged and the reproducibility was expressed as the coefficient of variability.

In a fourth group of subjects, the influence of alteration of electrode position was studied. Electrodes were placed initially in the recommended positions and moved sequentially by 5-cm increments in the frontal, sagittal and diagonal planes. TFI, SV and $\dot{Q}$ were recorded with each electrode configuration, and an average of six consecutive readings compared with those measured with electrodes in the recommended positions.

Comparison of TEB with thermodilution

The second part of the evaluation consisted of a comparison of simultaneous measurements of SV and $\dot{Q}$ by thoracic electrical bioimpedance (TEB) and thermodilution (TD) methods. Local Hospital Ethics Committee approval was obtained.

The patients investigated were admitted to the Intensive Care Unit (ITU) and had pulmonary

artery (PA) catheters inserted and cardiac output measurements made for clinical indications. Patients were excluded if they were in septic shock, had severe arrhythmias, or were too unstable. Thermodilution measurements were made using ice cold saline 10 ml at end-expiration. Cardiac output was calculated using the standard commercially available American Edwards Cardiac Output Computer (COM-1). All measurements were taken as the average of three consecutive readings, and the data used only if there was less than 10% variation between the readings. Thoracic electrical bioimpedance (TEB) measurements were made using the BoMED NCCOM3 as described earlier, with the electrodes placed in the recommended positions. TEB measurements were made as an average of 16 beats, and the readings were made simultaneously with the TD readings. Thus three TEB readings were averaged (giving $3 \times 16 = 48$ beats) to correspond to one TD reading.

Data were analysed to determine the correlation coefficient between the two methods by estimating SV and $\dot{Q}$, and the presence of bias was assessed by the method described by Bland and Altman [14]. In addition, an assessment of the ability of TEB to follow haemodynamic trends was made by examining the bias plots for individual patients.

Data handling. Data measured by the different techniques were compared using the correlation analysis and the Wilcoxon matched pairs signed ranks test; data recorded using different electrodes in the same subjects were compared using the sign test and Wilcoxon test. Data are presented as mean (SD) or mean (range), unless otherwise indicated.

Statistical significance was assumed at $P < 0.05$.

RESULTS

Volunteer Studies

Individual variability

Reproducibility during supine period at rest. Sixteen healthy volunteers (age 19–55 yr; weight 51–81 kg) were studied. Resting heart rates (HR) and mean arterial pressures (MAP) varied between 51 and 88 beat min^{-1} and 76 and 104 mm Hg, respectively.

The mean resting thoracic fluid indices (TFI) for all subjects was 26.2 (SD 0.26) Ω . The range of

individual coefficients of variation (CV) for TFI was 0.4–1.8%. Resting mean stroke volumes (SV) and cardiac outputs ($\dot{Q}$) varied between 66 and 180 ml, and 4.7 and 10.5 litre min^{-1} . The average coefficients of variation (calculated as the mean of the individual CV when determined from the seven sets of observations collected over the 30-min study period) are shown in table I. There were no differences in the magnitude of the CV for any of the four haemodynamic variables.

Reproducibility during supine period at rest on four different occasions. Nine male subjects (age 28–42 yr; weight 60–87 kg) were studied at rest on four occasions to assess variability in TFI, HR, SV and $\dot{Q}$ with time. All measurements were made using Medicotest ECG electrodes. The average values for each subject, calculated from the mean of each of the four separate occasions, were calculated; each individual data set being the mean of 10 bioimpedance readings. The intra-individual average for TFI over the four occasions varied between 22.5 and 29.3 Ω ; the average CV was 5.6% (range 1.9–13.1%).

The inter-day coefficients of variation for the other variables were: HR, average CV 7.5%, range of individual CV 4.6–11.0%; SV, average CV 10.9%, range 6.1–14.8%; $\dot{Q}$, average CV 8.7%, range 2.1–17.5%.

Influence of electrode type on TFI and SV

The influence of electrode type on TFI (and calculated SV) was assessed in 10 subjects on 44 occasions; for each data set TFI and SV were the mean of 10 readings following a period of 20 min resting supine.

There was a significant difference between values for TFI (mean values for TFI were 26.9 (SD 2.4) Ω and 25.3 (2.2) Ω , respectively, for RedDot and Medicotest electrodes ($P < 0.001$)); the mean

TABLE I. Mean values for each haemodynamic variable, average coefficient of variation (CV) and range of CV for all 16 subjects studied on a single occasion over a 30-min period at rest. MAP = Mean arterial pressure (calculated as systolic pressure + 2 diastolic pressure/3); HR = heart rate; SV = stroke volume; $\dot{Q}$ = cardiac output

	Mean	CV (%)	Range of CV (%)
MAP (mm Hg)	88.5	3.4	2.2–7.0
HR (beat min^{-1})	65	4.8	2.7–9.7
SV (ml)	110	4.7	2.1–8.5
$\dot{Q}$ (litre min^{-1})	7.0	5.1	2.6–9.7

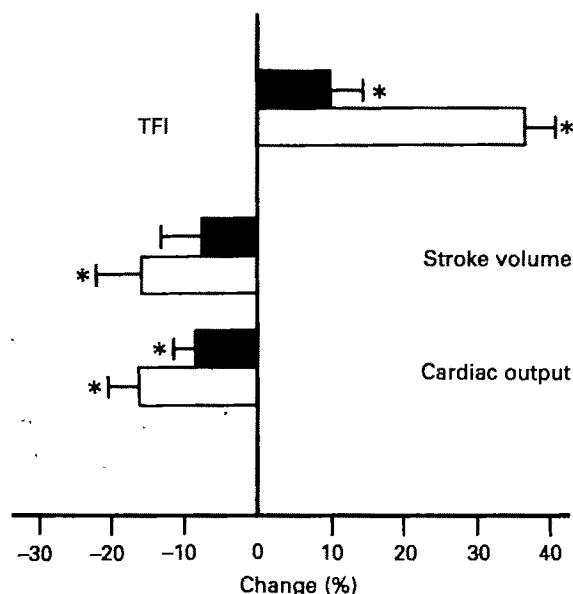


FIG. 1. Effect of alteration in electrode position in six subjects. Mean (SD) % change in TFI, SV and $\dot{Q}$ compared with values obtained with the electrodes in the "manufacturer recommended" position. ■ = 5-cm increase; □ = 10-cm increase of the effective thoracic length. * $P < 0.05$ compared with the recommended position.

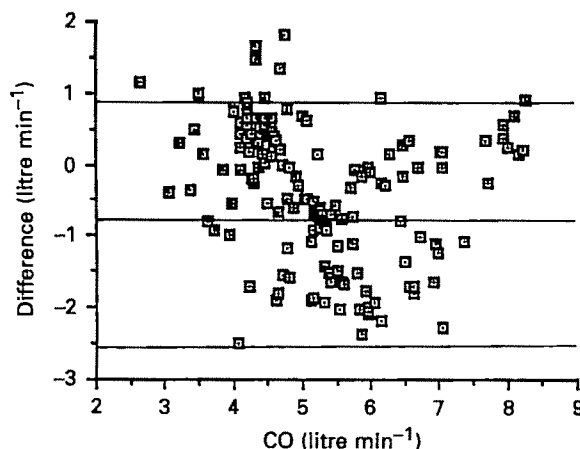


FIG. 2. Bias plot of all data points from the 16 intensive care unit patients. Average value of thermomodulation and thoracic electrical bioimpedance cardiac output (CO) vs difference (thermomodulation minus thoracic electrical impedance). Limits shown are the mean difference and the 95% confidence limits.

values for stroke volume were 125.0 (32.1) ml and 128.9 (34.1) ml, respectively (ns). The mean difference between electrode types for TFI (the fundamental parameter) was 1.64 (1.93) Ω

(RedDot minus Medicotest); the range of differences was -2.0 to 4.5Ω . This resulted in a mean difference for SV of 4.0 ml (range of differences -39 to 38 ml).

Influence of electrode position

In six volunteers (age 20–42 yr; weight 54–78 kg), the influence of changing the position of the sensing and current injecting electrodes was studied (fig. 1). Alterations in electrode position in either the diagonal or frontal planes resulted in less than 5% changes in TFI and SV. Likewise, changes of electrode position such that the effective inter-electrode position was increased by 5 cm by movement of the cervical electrodes also resulted in less than 5% changes in TFI and SV.

When the inter-electrode distance was increased by 5 cm by movement of the thoracic electrodes, there was a mean increase in TFI of 9.8% ($P < 0.05$), and decrease in SV of 7.5% (ns). These changes were of the same magnitude as those of the coefficients of variation found in the first group of subjects studied. However, when the inter-electrode distance was increased by 10 cm, there was a mean increase in TFI of 39.8% ($P < 0.05$) and mean decreases in SV of 15.8% ($P < 0.05$).

Patient Studies

Comparison of bioimpedance with thermodilution

Sixteen patients in the ICU were studied during controlled ventilation after aortic surgery, after abdominal surgery or for acute respiratory failure. No patient had clinical signs of systemic sepsis. The data collected provided 160 simultaneous measurements of cardiac output ($\dot{Q}$) and stroke volume (SV).

The mean (SEM) $\dot{Q}$ by bioimpedance was 5.63 (1.10) litre min^{-1} , compared with a mean of 4.38 (0.72) litre min^{-1} for thermodilution. The correlation of the two methods for cardiac output yielded the equation $\dot{Q}_{\text{TEB}} = 0.853 \times \dot{Q}_{\text{TD}} + 1.13$ and a correlation coefficient $r = 0.72$ ($P < 0.001$). The mean (SEM) SV by bioimpedance was 68.8 (18.9) ml compared with a mean of 55.8 (16.3) ml measured by thermodilution. The corresponding equation for stroke volume was $\text{SV}_{\text{TEB}} = 1.009 \times \text{SV}_{\text{TD}} + 6.84$, with a correlation coefficient $r = 0.83$ ($P < 0.001$). However, the correlation coefficient describes only the association of one method with another; not the agreement of the results. Therefore the difference between measurements (TD minus TEB) was plotted

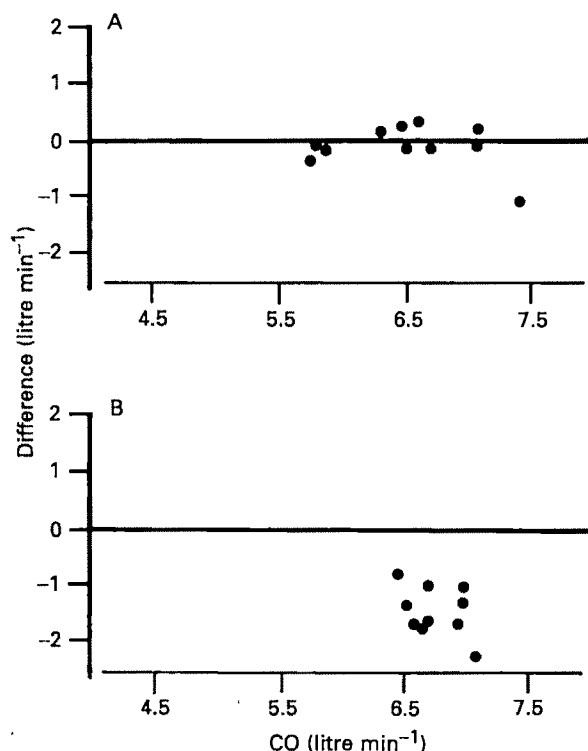


FIG. 3. Individual bias plots for two representative patients. A: Constant bias found in most patients; B: variable bias as a result of the intrinsic variability found in a given individual for repeated determinations of a constant cardiac output. CO = cardiac output (average value of thermodilution and thoracic electrical bioimpedance); Difference = (thermodilution minus thoracic electrical impedance).

against the corresponding means of the two methods $[(TD + TEB)/2]$ together with the 95% confidence limits (fig. 2). The mean difference for cardiac output was -0.86 (-2.6 to $+0.89$) litre min^{-1} and that for stroke volume -13 (-35.2 to $+9.2$) ml.

Figures 3A and B show individual bias plots representative of two different groups of patients. Most patients showed a constant bias for both $\dot{Q}$ and SV (fig. 3A). Here the patient has a bias of -0.15 litre min^{-1} over a range of $\dot{Q}$ values between 5.7 and 7.4 litre min^{-1} . However, in a few patients there was an apparent variable bias (fig. 3B). In these patients, the range over which cardiac output measurements have been recorded was narrow.

DISCUSSION

The major advantage of the thoracic electrical bioimpedance (TEB) method for measuring cardiac output ($\dot{Q}$) and stroke volume (SV) is the ease

with which it can be learnt and applied by the clinician. The NCCOM3 also has the advantage of on-line analysis and the provision of beat-to-beat information.

Our results showed that for normal subjects the variability of TEB measurement of $\dot{Q}$ and SV was of the same magnitude as for other cardiovascular variables (e.g. HR and MAP). Similar estimates for variability have been reported by Veigl and Judy using the earlier Minnesota Impedance Cardiograph [15] and Wong and colleagues [16]. Dye dilution and thermodilution methods of measuring cardiac output give comparable estimates of variability: Fischer and colleagues [17] reported a variability of 7% for $\dot{Q}$ measured by dye dilution and while Sleeper and colleagues [18] showed a variability of 6% for dye dilution if the same arterial site was used for sampling, but a variability of 20% if different arteries were used for sampling. The variability of thermodilution depends on several factors, including volume and temperature of injectate and relationship to the ventilatory cycle. Stevens and colleagues [19] reported a coefficient of variation of 4% for thermodilution measurements when they were timed to peak inspiration or end-expiration; but 10% if the injections were made randomly throughout the ventilatory cycle. Runciman, Ilsley and Roberts [20], in a detailed examination of the factors affecting variability of thermodilution, concluded that, despite attention to detail, a 10% variability in cardiac output measurement existed when compared with dye dilution techniques. Stetz and colleagues [21] investigated the reproducibility of commercially available thermodilution devices, and concluded that there must be a minimum difference of 12–15% between triplicate determinations of $\dot{Q}$ to suggest a change of clinical significance. Our coefficients of variation were 4.7% for SV and 5.1% for $\dot{Q}$ over a single 30-min study period.

Inter-day variability was greater. This reflects, in part, normal physiological variations for which it is virtually impossible to standardize (e.g. factors such as the time of day, relationship to ingestion of food and emotional state affect basal or resting cardiac output). Coefficients of variation for SV and $\dot{Q}$ of 10.2% and 8.5%, respectively, again compare well with those reported by Veigl and Judy [15].

One of the main sources of observer error of the TEB method relates to the placement of the electrodes and the electrode type. Alteration of

electrode type in normal healthy volunteers gave changes of 19 %, 22 % and 19 %, respectively, for TFI, SV and $\dot{Q}$. One explanation may be that different electrode types change the skin-electrode interface which would, in turn, affect the dynamic component of the impedance signal.

Any alteration in electrode position should alter Z_0 as this is proportional to L —the length of the volume conductor through which the impedance changes are measured. The NCCOM3 uses the Bernstein-Sramek formula [9], where SV is proportional to VEPT, and inversely proportional to Z_0 . VEPT is proportional to H^3 which is proportional to L^3 . Therefore SV and $\dot{Q}$ are proportional to L^2 . If the normal inter-electrode distance is assumed to be 30 cm, an increase in the distance by 5 cm should increase SV (and hence $\dot{Q}$) by 26 %, and an increase of 10 cm should result in an increase in SV of 40 %. These are much larger than the changes of 8 % and 16 % we recorded with changes in electrode position. This is caused by the internal algorithm in the NCCOM3 [9] which includes the factor d —a correction factor for changes in the body habitus from ideal. The magnitude of dZ/dt_{max} is dependent also upon the sensing electrode distance and the value of Z_0 [9, 22, 23].

Other studies have compared the TEB method for determining $\dot{Q}$ and SV with TD [6, 8, 10–13, 24], dye dilution [3, 4], the direct Fick method [7, 25], the indirect Fick (carbon dioxide rebreathing) method [26] and Doppler ultrasound [8, 13, 25, 27]. There has been wide variation in the reported correlation coefficients for TEB against TD—from 0.41 [28] to 0.93 [6]. These differences can be attributed, in part, to the different populations studied.

Another factor contributing to the variation in correlation coefficients is the different reference techniques used for comparison. These all have their own variability and sources of inaccuracy [17, 19–21]. Even the direct Fick method has been shown to have a variability of around 8 % [29]. These sources of variability and inaccuracies are not necessarily the same as those of the technique being investigated and thus, in comparisons, differences may be compounded. None of the reference techniques is therefore a true “gold standard”, while the correlation coefficient reflects only a measure of association between two methods, not agreement.

A more relevant way to assess agreement is to construct a bias plot examining the variability

between the two methods over the whole range of results [14]. Our data show a variable bias for $\dot{Q}$, with 95 % confidence limits of -2.6 to $+0.89$ litre min^{-1} . This is a larger range than that reported by Northridge and colleagues [27] for spontaneously breathing patients after infarction, but similar to the values of Wong and colleagues [8] and Siegel and colleagues [13].

Wong noted the best agreement between bio-impedance and thermal dilution in patients who had not undergone aortic or open heart surgery [18]. In these patients, errors may occur because of intrathoracic fluid shifts, aortic manipulation or changes in PCV. Wong also noted that mechanical ventilation (as in all of our patients) had no effect on the agreement between the measurement techniques. In comparison with the study by Northridge and colleagues [27], the greater variability in our study reflects the larger number of comparisons (160 vs 25 data points) and a greater range of cardiac output ($\dot{Q}$) values (2.6–8.5 litre min^{-1} compared with 1.1–6.2 litre min^{-1}).

Our results suggest that TEB overestimates at low and underestimates at high values of cardiac output, despite the NCCOM3 having an internal algorithm which is designed to compensate for these changes in dZ/dt_{max} at low cardiac outputs. An explanation for this phenomenon may be the alteration in distribution of blood flow in the thorax at low and high cardiac outputs, which in turn may lead to alterations in the relative contributions of the various impedance changes making up the global impedance change measured by the NCCOM3 [9]. These discrepancies between the two methods for cardiac output measurement may further lie in the different physical principles utilized by the techniques; and hence a good correlation under one set of physiological circumstances (e.g. IPPV) may not be seen under another (e.g. spontaneous ventilation).

REFERENCES

1. Kubicek WG, Karegis JN, Patterson RP, Witsoe DA, Matteson RH. Development and evaluation of an impedance cardiac output system. *Aerospace Medicine* 1966; 37: 1208–1212.
2. Brooksby I. Impedance cardiography—comparative studies during cardiac catheterization. *Proceedings of Symposium on Impedance Cardiography, Royal College of Surgeons, London*, 1975: 1–16.
3. Secher NL, Arnsbo P, Heslet Anderson L, Thomsen A. Measurements of cardiac stroke volume in various body positions in pregnancy and during Caesarean section: a comparison between thermodilution and impedance

- cardiography. *Scandinavian Journal of Clinical and Laboratory Investigation* 1979; 39: 569-576.
4. Milsom I, Forssman L, Biber B, Dottori O, Sivertsson R. Measurement of cardiac stroke volume during Caesarean section: a comparison between impedance cardiography and the dye dilution technique. *Acta Anaesthesiologica Scandinavica* 1983; 27: 421-426.
 5. Hatcher DD, Srb OD. Comparison of two noninvasive techniques for estimating cardiac output during exercise. *Journal of Applied Physiology* 1986; 61: 155-159.
 6. Donovan KD, Dobb GJ, Woods WP, Hockins BE. Comparison of transthoracic electrical impedance and thermodilution methods for measuring cardiac output. *Critical Care Medicine* 1986; 14: 1038-1044.
 7. Miles DS, Gotshall RW, Golden JC, Tuuri DT, Beckman RH, Dillon T. Accuracy of electrical impedance cardiography for measuring cardiac output in children with congenital heart disease. *American Journal of Cardiology* 1988; 61: 612-616.
 8. Wong DH, Tremper KK, Stemmer EA, O'Connor D, Wilbur S, Zaccari J, Reeves C, Weidoff P, Trujillo RJ. Noninvasive cardiac output: Simultaneous comparison of two different methods with thermodilution. *Anesthesiology* 1990; 72: 784-792.
 9. Bernstein DP. A new stroke volume equation for thoracic electrical bioimpedance: Theory and rationale. *Critical Care Medicine* 1986; 14: 904-909.
 10. Appel PL, Kram HB, Mackabee J, Fleming AW, Shoemaker WC. Comparison of measurements of cardiac output by bioimpedance and thermodilution in severely ill surgical patients. *Critical Care Medicine* 1986; 14: 933-935.
 11. Spinale F, Reines HD, Crawford FA. Comparison of bioimpedance and thermodilution methods for determining cardiac output: Experimental and clinical studies. *Annals of Thoracic Surgery* 1988; 45: 421-425.
 12. Sullivan PJ, Martineau RJ, Hull KA, Miller DR. Comparison of bioimpedance and thermodilution measurements of cardiac output during aortic surgery. *Canadian Journal of Anaesthesia* 1990; 37: s78.
 13. Siegel LC, Shafer SL, Martinez GM, Ream AK, Scott JC. Simultaneous measurements of cardiac output by thermodilution, esophageal Doppler and electrical impedance in anesthetized patients. *Journal of Cardiothoracic Anesthesia* 1988; 2: 590-595.
 14. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307-310.
 15. Veigl VL, Judy WV. Reproducibility of haemodynamic measurements by impedance cardiography. *Cardiovascular Research* 1983; 17: 728-734.
 16. Wong DH, Onishi R, Tremper KK, Reeves C, Zaccari J, Wong AB, Miller JB, Cordero V, Davidson J. Thoracic bioimpedance and Doppler cardiac output measurement: learning curve and inter-observer reproducibility. *Critical Care Medicine* 1989; 17: 1194-1198.
 17. Fischer AP, Benis AM, Jurado RA, Seely E, Teirstein P, Litwak RS. Analysis of the errors in measurement of cardiac output by simultaneous dye dilution and thermal dilution in cardiosurgical patients. *Cardiovascular Research* 1978; 12: 190-199.
 18. Sleeper JC, Thompson HK jr, McIntosh HD, Elsten RC. Reproducibility of results obtained with indicator dilution techniques for estimating cardiac output in man. *Circulation Research* 1962; 11: 712-720.
 19. Stevens JH, Raffin TA, Mihm FG, Rosenthal MH, Stetz CW. Thermodilution cardiac output measurement: Effects of the respiratory cycle on its reproducibility. *Journal of the American Medical Association* 1985; 253: 2240-2242.
 20. Runciman WB, Ilsley AH, Roberts JG. An evaluation of the thermodilution cardiac output measurement using the Swan-Ganz catheter. *Anaesthesia and Intensive Care* 1981; 9: 208-220.
 21. Stetz CW, Miller RG, Kelly GE, Raffin TA. Reliability of the thermodilution method in determinations of cardiac output in clinical practice. *American Review of Respiratory Diseases* 1982; 126: 1001-1004.
 22. Yamakoshi K, Togawa T, Ito H. Evaluation of the theory of cardiac output computation from transthoracic impedance plethysmogram. *Medical and Biological Engineering and Computing* 1979; 17: 697.
 23. Djordjevic L, Sadove MS. Experimental study of the relationship between the base impedance and its time derivative in impedance plethysmography. *Medical Physics* 1981; 8: 76.
 24. Shoemaker WC, Appel PL, Kram HB, Nathan RC, Thompson JL. Multicomponent noninvasive physiological monitoring of circulatory function. *Critical Care Medicine* 1988; 16: 482-490.
 25. Goli VD, Teague SM, Prasad R, Harvey J, Voyles WF, Olson EG, Schechter E, Thadani U. Noninvasive evaluation of aortic stenosis severity utilizing Doppler ultrasound and electrical bioimpedance. *Journal of the American College of Cardiology* 1988; 11: 66-71.
 26. Smith SA, Russell AE, West MJ, Chalmers J. Automated non-invasive measurement of cardiac output: comparison of electrical bioimpedance and carbon dioxide rebreathing techniques. *British Heart Journal* 1988; 59: 292-298.
 27. Northridge DB, Findlay IN, Wilson J, Henderson E, Dargie HJ. Non-invasive determination of cardiac output by Doppler echocardiography and electrical bioimpedance. *British Heart Journal* 1990; 63: 93-97.
 28. Preiser JC, Daper A, Parquier J-N, Contempe B, Vincent J-L. Transthoracic electrical bioimpedance versus thermodilution technique for cardiac output measurement during mechanical ventilation. *Intensive Care Medicine* 1989; 15: 221-223.
 29. Selzer A, Sudrann RB. Reliability of the determination of cardiac output in man by means of the Fick principle. *Circulation Research* 1958; 6: 485-490.

PRESSURE SUPPORT VENTILATION USING A NEW TRACHEAL GAS INJECTION TUBE

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SUMMARY

In order to explore new types of jet ventilation, we tested a tracheal gas injection tube (TGIT) which included six thin capillaries and provided high pressure injection. The driving pressure was chosen to yield a plateau of inspiratory tracheal pressure of 10 cm H₂O. An original controller was built to monitor spirometry and trigger injection in order to deliver both pressure controlled ventilation (PCV_{TGIT}) and a new mode of inspiratory pressure support jet ventilation (IPS_{TGIT}). The PCV_{TGIT} mode maintained the same end-tidal carbon dioxide concentration as conventional ventilation with the same tidal and minute ventilation. We studied 10 patients after abdominal surgery. During spontaneous breathing, the patients were allowed to breathe through the tube, successively with and without IPS_{TGIT}. IPS_{TGIT} compared with spontaneous breathing increased minute ventilation (from 5.7 (SD 1.6) to 7.1 (1.7) litre min⁻¹) ($P < 0.001$). It reduced the total work of breathing (from 0.625 (0.223) to 0.263 (0.151) J litre⁻¹, respectively) ($P < 0.01$) and the occlusion pressure (from 2.62 (1.28) to 1.36 (0.74) cm H₂O, respectively) ($P < 0.01$). It is concluded that this TGIT used with a specific system for sensing and triggering ventilation allows inspiratory pressure support during low frequency jet ventilation.

KEY WORDS

Equipment: tracheal gas injection tube. Ventilation: jet ventilation.

Mechanical ventilation is often required in the period after major surgery. Residual effects of anaesthesia [1], abdominal pain [2] and diaphragmatic dysfunction [3] may contribute to depressed ventilation after operation and impair spon-

taneous breathing. To overcome these problems, conventional artificial ventilation may be used after operation, followed by an assisted mode such as inspiratory pressure support (IPS), which is a pressure limited mode. IPS is provided by ventilators, using sophisticated servo control techniques. We described a new tracheal gas injection tube (TGIT) which was able to produce high velocity jets at its distal tip and consequently to generate positive pressure by air momentum transfer down to the injection site [4, 5]. This system was used successfully for apnoeic ventilation during cardiopulmonary resuscitation in animals [6], and man [7] and to prevent oxygen desaturation during apnoeic periods in patients undergoing mechanical ventilation [8]. We have also developed a new electronic system which may be coupled to the TGIT to produce either pressure controlled ventilation (PCV_{TGIT}) or inspiratory pressure support (IPS_{TGIT}). The aim of this study was to examine high flow jet ventilation in both controlled and spontaneous ventilation.

PATIENTS AND METHODS

Patients and anaesthesia

We studied 10 patients (five males) (mean age 61 (SD 11) yr; weight 65 (6) kg; height 167 (7) cm; non-smokers; ASA I or II) in the recovery room after abdominal surgery. Surgery was performed under general anaesthesia with fentanyl 3 µg kg⁻¹, flunitrazepam 0.03 mg kg⁻¹ and vecuronium 0.1

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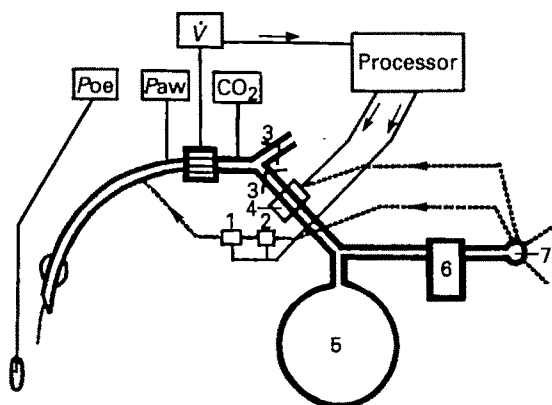


FIG. 1. System used with the TGIT. A pneumotachograph measured the flow ($\dot{V}$) passing through the lumen of the TGIT. The flow signal was adapted by an analog system (Processor) to trigger injection via electronic valves (1, 2). The system also included unidirectional valves on both branches of the Y-piece (3), a pneumatic valve with solenoid for occlusion pressure measurement (4), a rubber reservoir bag (5), a humidifier (6) and an air-oxygen mixer and pressure regulator (7). Tracheal pressure (P_{aw}) was measured by a catheter inside the trachea and oesophageal pressure (P_{oe}) via a balloon tipped catheter.

mg kg⁻¹ for induction and tracheal intubation. Anaesthesia was maintained with 70% nitrous oxide in oxygen and administration of increments of the same drugs. Patients' lungs were ventilated perioperatively by a volume cycled ventilator (Draeger, SA₁) in a conventional mode.

Material and signal processing

The system we used comprised the following components (fig. 1):

A TGIT (fig. 2) (Porgès laboratories, Le Plessis Robinson, France) of 8 mm i.d. with a low pressure cuff. In its wall, six thin capillaries (diameter: 720 μ m) are moulded by extrusion. These are distributed evenly around the circumference and emerge on the internal aspect of the TGIT, 1 cm before its distal tip. These capillaries are connected to an adjustable high pressure air-oxygen source (driving pressure 0–3 bar) to produce high velocity gas injection at the TGIT distal end, as described previously [8]. The performances of the TGIT were tested in our laboratory before the clinical study. The relationship between the driving pressure and the flow of the injectors was found to be constant for all TGIT. The pressure generated by the TGIT in the trachea (measured at the carinal level) ranged between 0 and 27 cm H₂O according to the driving pressure used (0–3.5 bar). For instance, a driving pressure of 1.2 bar caused a flow of 350 ml s⁻¹ through the injectors and this generated a pressure of 10 cm H₂O in the trachea.

An inspiratory line with an air-oxygen mixer, a pressure regulator, a cascade humidifier (Fisher-Paykell, MR 428, New Zealand), a 3-litre rubber reservoir which served as a mixing chamber to allow a constant $F_{I_{O_2}}$ and a unidirectional valve. From the air-oxygen mixer a line supplied high pressure gas to the capillaries of the TGIT via a solenoid valve (opening-closing delay: 11 ms). An occluding pneumatic valve was used to measure the occlusion pressure 0.1 s after the beginning of inspiration ($P_{0.1}$) [9]. This valve comprised a latex balloon mounted inside a short, 22-mm diameter tube placed in the inspiratory line. This balloon

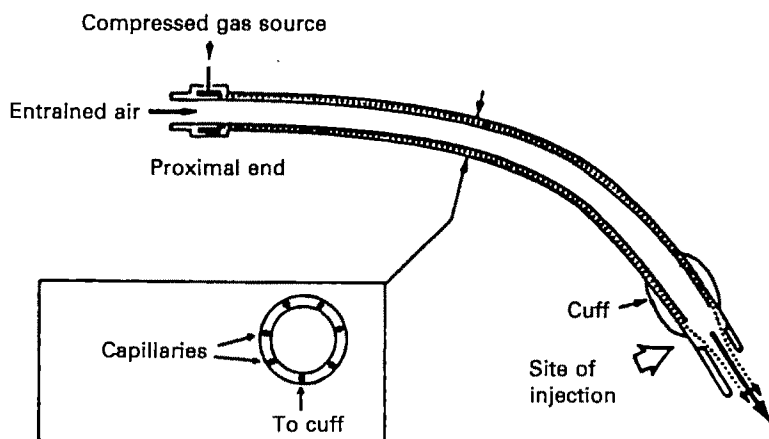


FIG. 2. The tracheal gas injection tube (TGIT).

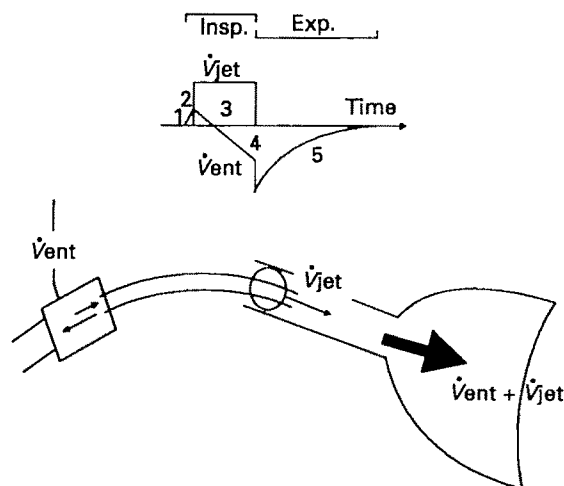


FIG. 3. Flow regimen during ventilation by the TGIT. Top: The flow of the jets ($\dot{V}_{jet}$) and that measured at the airway opening ($\dot{V}_{vent}$) are displayed against time. The different phases of the breathing cycle are: (1) onset of spontaneous inspiration when $\dot{V}_{vent}$ increases until the injection (2) is triggered, resulting in a constant flow ($\dot{V}_{jet}$) produced by the injectors (3). During the injection phase (3) $\dot{V}_{vent}$ becomes negative resulting from opening of $\dot{V}_{jet}$ to atmosphere via the TGIT. When injection stops (4) at the onset of expiration, the flow recorded by the pneumotachograph is measured by $\dot{V}_{vent}$. Bottom: The true flow signal corresponds to the algebraic sum of that measured at the airway opening ($\dot{V}_{vent}$) and the constant flow of the jets ($\dot{V}_{jet}$) represented by a calibrated electronic signal. During expiration, the flow of the jets is nil and $\dot{V}_{Pt}$ equals $\dot{V}_{vent}$.

was linked to a 0.5-bar pressure source via a three-way electric solenoid valve. The valve was operated by the servo controller. Occlusion was triggered by pressing an occlusion button to inflate automatically the balloon located on the inspiratory limb, during the next expiration. The controller kept the valve inflated during the first 100 ms of the following inspiration.

The expiratory line included a unidirectional valve.

An analog controller was used to measure the gas volumes and to trigger injection in the TGIT, via the solenoid valve, in the mode specific for each of the two ventilation methods tested (PCV_{TGIT} or IPS_{TGIT}). Measurement of gas volumes necessitated signal processing. Indeed, during injection (inspiration) the flow received by the patient ($\dot{V}_{Pt}$) corresponded to the algebraic sum of the flow of the jets ($\dot{V}_{jet}$), which is constant throughout inspiration, and that of entrained gas ($\dot{V}_{vent}$) (fig. 3) [10–12]. Therefore, during injection, we measured $\dot{V}_{vent}$ at the TGIT proximal opening (Fleish No. 1 pneumotach-

graph Lausanne, Switzerland, and Validyne MP 45, ± 2.5 cm H₂O, Northridge, California) and added to this signal a constant voltage representing $\dot{V}_{jet}$ in order to obtain $\dot{V}_{Pt}$. Tidal volume was obtained by integration of $\dot{V}_{Pt}$ (Gould, ES1000). In contrast, expiration was passive and $\dot{V}_{jet}$ nil. At this time, $\dot{V}_{Pt}$ corresponded to the flow measured by the pneumotachograph. The accuracy of the tidal volume reconstruction from $\dot{V}_{jet}$ and $\dot{V}_{vent}$ had been assessed previously. Error did not exceed $\pm 1.5\%$.

In PCV_{TGIT} the controller triggered injection according to the ventilatory frequency rate and inspiratory time selected, by means of an internal clock controlling the injection solenoid valve. Expiration was passive and started from the end of injection.

IPS_{TGIT} required spontaneous breathing. In this case, injection was started after the onset of inspiration—that is, when $\dot{V}_{Pt}$ exceeded 100 ml s⁻¹, and stopped when it decreased to less than 25% of its peak inspiratory value (fig. 4). The controller monitored tidal volume (integration of $\dot{V}_{Pt}$) in the same way as in PCV. In both modes, expiration occurred freely and tracheal pressure (P_{aw}) returned to atmospheric before injection resumed at the next breath. No self-cycling was observed during the triggering of IPS_{TGIT}.

The mixing of the jets in the trachea has been studied previously on a tracheal model and appeared to be complete within the first 2 cm distal to the TGIT tip. Hence, in order to measure P_{aw} in conditions unaffected by injection, it was measured via a 1-mm i.d. catheter inserted down the trachea, 5 cm below the TGIT tip, which was connected to a pressure transducer (Validyne MP 45, ± 30 cm H₂O). Oesophageal pressure (P_{oe}) was measured using a balloon catheter and a transducer (Validyne MP 45, ± 30 cm H₂O). The position of the oesophageal catheter was checked by an occlusion test [13]. Respiratory gas was sampled continuously (150 ml min⁻¹) at the Y-piece for end-tidal (PE'_{CO_2}) measurement (Gould, Mark IV). All signals were recorded on an eight-channel paper chart recorder (Gould, ES1000) at 25 mm s⁻¹ during each set and at 200 mm s⁻¹ during measurement of $P_{0.1}$.

Procedure

The experimental study was conducted in the recovery room during the early postoperative period. Informed consent was obtained from all

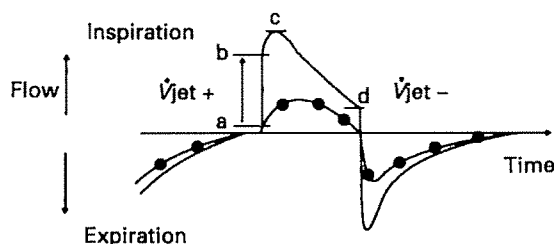


FIG. 4. Comparison between $\dot{V}_{Pt}$ with and without (spontaneous breathing) (●) IPS_{TGIT} . $\dot{V}_{jet}$ induces a brisk increase of inspiratory flow (a to b). It ceases when $\dot{V}_{Pt}$ is 25% (d) of its peak inspiratory value (c). Expiratory flow is greater in IPS_{TGIT} because of a larger volume of the breath.

patients and the study was approved by the local Ethics Committee. It comprised two parts.

Controlled mode ventilation. The first part was performed before the return of spontaneous breathing. First the patient received controlled mode ventilation (CMV) and a CPU₁ ventilator (Ohmeda, France) with standard settings, during a resting period of 30 min. Then the patient was allocated randomly to one 15-min period of CMV on the CPU₁ ventilator and to one period of PCV_{TGTT} generated by gas injection in the TGIT with the patient's lungs disconnected from the ventilator. The settings chosen for the two modes were identical ($\dot{V}_T = 8 \text{ ml kg}^{-1}$, ventilatory frequency 14 b.p.m., $T_I/T_T = 33\%$, no PEEP, $FI_{O_2} = 0.40$). Therefore, $\dot{V}_T$ in PCV_{TGTT} was controlled by adjusting the driving pressure. At the end of each period and after steady state was achieved, Paw , $\dot{V}_{Pt}$, $\dot{V}_T$ and PE'_{CO_2} signals were recorded and averaged over 3 min. All patients underwent ventilation passively at the selected settings without spontaneous ventilation whilst still under the influence of residual anaesthesia.

Inspiratory pressure support. The second part of the study was initiated when spontaneous breathing resumed. Then 15-min periods of spontaneous breathing and IPS_{TGIT} were allowed at random,

using the TGIT without a conventional ventilator. The IPS pressure was set to reach a plateau of 10 cm H₂O by adjusting the driving pressure. At the end of each period the flow, pressure and carbon dioxide signals were recorded. They were averaged over 3 min in steady state conditions in order to obtain: ventilatory frequency (f), $\dot{V}_{Pt}$, $\dot{V}_T$, Paw , Poe and PE'_{CO_2} . Five occlusion tests were performed and averaged to assess $P_{0.1}$. From these signals, minute expiratory volume ($\dot{V}_E$) was computed as the product of f and $\dot{V}_T$ and PE'_{CO_2} was calculated from the carbon dioxide trace. The work of breathing was computed automatically (Apple IIe) as described previously [14], using Poe and $\dot{V}_{Pt}$ signals to calculate the corresponding work (W_{oe}).

Statistical analysis

Results are expressed as mean (SD). Comparisons between mean values of each mode of ventilation were performed using paired t tests [15].

RESULTS

In the first part of the study, when the tracheal gas injection tube was used in PCV_{TGTT} mode, it appeared to be as efficient as a conventional ventilator. Indeed, using the same ventilatory settings, the alveolar ventilation achieved was identical in the two modes, as assessed by equal values of PE'_{CO_2} (4.48 (0.77) kPa compared with 4.64 (0.77) kPa (ns)). In contrast, the peak pressures differed slightly between PCV_{TGTT} and CMV (11.7 (6.0) cm H₂O and 14.1 (7.0) cm H₂O, respectively), but this was not statistically significant. This difference in peak pressures could be caused by differences in flow profile which would cause different pressure changes across the respiratory resistance.

TABLE I. Lung volumes and PE'_{CO_2} in spontaneous breathing

	f (b.p.m.)	T_I/T_T (%)	T_I (s)	T_E (s)	$\dot{V}_T$ (ml)	$\dot{V}_E$ (litre min ⁻¹)	PE'_{CO_2} (kPa)	Paw (cm H ₂ O)
Without IPS_{TGIT}								
Mean	14	33	1.4	3.2	442	5.7	5.65	-4.9
SD	5	9	0.2	1.3	188	1.6	0.72	2.4
With IPS_{TGIT}								
Mean	13	29	1.3	3.5	557	7.1	4.88	9.7
SD	4	9	0.2	1.5	181	1.7	0.68	1.4
P	ns	ns	ns	ns	< 0.01	< 0.001	< 0.05	< 0.001

TABLE II. Occlusion pressure and work of breathing

	$P_{0.1}$ (cm H ₂ O)	W_{oe} (J litre ⁻¹)
Without IPS _{TGIT}		
Mean	2.62	0.625
SD	1.28	0.223
With IPS _{TGIT}		
Mean	1.36	0.263
SD	0.74	0.151
P	< 0.01	< 0.01

In the second part of the study, the 10 cm H₂O IPS_{TGIT} delivered by our TGIT gas injector increased ventilation in all patients in comparison with spontaneous breathing, as assessed by a 26 % increase in $\dot{V}_T$ and a 14 % decrease in Pe'_{CO_2} (table I). IPS_{TGIT} caused a reduction of the work of breathing as reflected by a 58 % decrease in W_{oe} which represents the total work of breathing performed by the patient, and $P_{0.1}$ was reduced by 48 % during IPS_{TGIT} compared with spontaneous breathing (table II).

DISCUSSION

We have described previously the theoretical principles of this new TGIT, based on the properties of turbulent jets in a confined tube [7]. From these studies it appeared that airway pressurization could be used efficiently in cardiac resuscitation [8] or to prevent hypoxaemia during tracheal aspiration in ARDS [9]. The present study was designed to test if the use of this technology could be extended to mechanical ventilation by taking advantage of the versatility of the TGIT as a pressure generator. The major advantages we expected of the TGIT compared with a conventional ventilator were absence of a demand valve which increases the work of breathing during early inspiration [16], the triggering function (based on detection of inspiration by the inspiratory flow at the TGIT proximal opening) appears to be more sensitive than inspiratory pressure [17, 18], and as gas injection is performed at the distal tip of the TGIT, it should become possible to suppress the component of inspiratory work caused by tube resistance [16].

In order to operate this new tracheal tube we had to develop a new control system to trigger injection and infer spirometry from $\dot{V}_{ent}$. This was made possible by taking advantage of the constant inspiratory flow delivered by the injec-

tors. This system appeared to work well and represents the key point of this study. It detected inspiration without self-cycling phenomena.

From the first part of this study, it appeared that efficient controlled ventilation was possible with the TGIT gas injector. The same Pe'_{CO_2} was achieved with the same tidal volume and minute ventilation in PCV and CMV, despite different flow patterns (constant in CMV and decelerating in IPS_{TGIT}), indicating that both modes of ventilation provided similar alveolar ventilation. Therefore we postulate that the gradient between Pa_{CO_2} and Pe'_{CO_2} was stable. This is true if the distribution of ventilation and perfusion was constant. Because the volumes insufflated were the same, we believe that perfusion did not change markedly between modes. Also, diffusion with jet ventilation [19–21] and deadspace are likely to be similar with both modes.

There are two reasons to explain the absence of significant changes between PCV_{TGIT} and CMV. First, in a laboratory study of the TGIT, Isabey and colleagues [5] showed that mixing from the jets was almost instantaneous—that is, it occurred in the first 2 cm distal to the TGIT tip. This fast mixing probably results from the lateral and circular position of the injectors, which differs from the coaxial or lateral injection sites used commonly in high frequency jet ventilation. Second, the low frequency of ventilation used in this study was much less than the frequency ranges at which increased diffusion phenomena have been described.

In the second part of our study, our patients showed the usual breathing pattern seen during early recovery from general anaesthesia and several patients had slightly depressed ventilation during spontaneous breathing, mainly because of reduced $\dot{V}_T$. The use of IPS_{TGIT} increased ventilation by reducing Pe'_{CO_2} and the work of breathing, similar to conventional pressure support. Indeed, the total work of breathing (W_{oe}) was reduced markedly. The unloading effect of IPS_{TGIT} was accompanied by a reduction in central respiratory output as assessed by the reduction in $P_{0.1}$. This adaptation of central respiratory drive by positive pressure unloading is consistent with the results of Poon, Ward and Whipp [22], who studied IPS during exercise in healthy volunteers.

In both modes, the system was tolerated well, as attested by absence of cough or tracheal irritation caused by the jets. The type of injection used was distal, in six capillaries. This differs from some

standard jet ventilation tubes which comprise a single large bore distal injection lumen. Therefore, the energy of each jet in our TGIT and the potential risk of tracheal damage may be less than that of a single distal jet.

We humidified only entrained gas, which represents a small proportion of the net inspiratory tidal volume. Therefore, the gas from the injectors should also be humidified if the TGIT is used for prolonged ventilation.

As with conventional jet ventilation, obstruction of the lumen of the tube may lead to barotrauma if injection is not controlled by a pressure alarm system. In our study, this was controlled manually by observing continuously the airway pressure trace. Our prototype has been developed further and includes a system which monitors *Paw* continuously via an additional capillary which has been moulded in the wall of the tube. Injection ceases if *Paw* overshoots or does not change during inspiration (implying that either the main lumen of the tube or the pressure capillary is obstructed).

REFERENCES

1. Rigg J. Ventilatory effects and plasma concentrations of morphine in man. *British Journal of Anaesthesia* 1978; 50: 759-764.
2. Becquemin JP, Piquet J, Becquemin MH, Mellièrè D, Harf A. Pulmonary function after transversal or midline incision in patients with obstructive pulmonary disease. *Intensive Care Medicine* 1985; 11: 247-251.
3. Dureuil B, Cantineau JP, Desmonts JM. Effects of upper or lower abdominal surgery on diaphragmatic function. *British Journal of Anaesthesia* 1987; 59: 1230-1235.
4. Isabey D, Boussignac G, Harf A. Increase in tracheal pressure during jet ventilation. *British Journal of Anaesthesia* 1989; 63: 71S-77S.
5. Isabey D, Boussignac G, Harf A. Effect of air entrainment on airway pressure during endotracheal gas injection. *Journal of Applied Physiology* 1989; 67: 771-779.
6. Brochard L, Adnot S, Bertrand C, Boussignac G, Harf A. Ventilatory and hemodynamic effects of cardiopulmonary resuscitation (CPR) during constant flow ventilation (CFV). *American Review of Respiratory Disease* 1988; 137: A295.
7. Brochard L, Boussignac G, Dubois-Randé JL, Harf A, Bertrand C, Geschwind H. Cardiopulmonary resuscitation without a ventilator using a novel endotracheal tube in human. *Anesthesiology* 1990; 72: 389.
8. Mion G, Brochard L, Mancebo G, Boussignac G, Isabey D, Harf A, Lemaire F. Prevention of arterial oxygen desaturation induced by endotracheal suctioning using constant flow insufflation. *Anesthesiology* 1988; 69: A179.
9. Whitelaw WA, Derenne JP, Milic-Emili J. Occlusion pressure as a measure of respiratory center output in conscious man. *Respiratory Physiology* 1975; 23: 181-199.
10. Jones MJ, Mottram SD, Lin ES, Smith G. Measurement of entrainment ratio during high frequency jet ventilation. *British Journal of Anaesthesia* 1990; 65: 197-203.
11. Young JD, Sykes MK. A method for measuring tidal volume during high frequency jet ventilation. *British Journal of Anaesthesia* 1988; 61: 601-605.
12. Abbrecht PH, Bryant HJ, Kyle RR, El Mawan T. Determinants of alveolar ventilation during high-frequency jet ventilation in dogs. *Critical Care Medicine* 1986; 14: 563-569.
13. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. *American Review of Respiratory Disease* 1982; 126: 788-791.
14. Beydon L, Chassé M, Harf A, Lemaire F. Inspiratory work of breathing during spontaneous ventilation using demand valves and continuous flow systems. *American Review of Respiratory Disease* 1988; 138: 300-304.
15. Schwartz D. *Méthodes Statistiques à l'Usage des Médecins et des Biologistes*, 3rd Edn. Paris, Flammarion: 1963.
16. Mecklenburgh JS, Latto IP, Al-Obaidi TA, Swai EA, Mapelson WW. Excessive work of breathing during intermittent mandatory ventilation. *British Journal of Anaesthesia* 1986; 58: 1048-1054.
17. Christopher KL, Neff TA, Bowman JL, Eberle DJ, Irvin CG, Good JT. Demand and continuous flow intermittent mandatory ventilation systems. *Chest* 1985; 87: 625-630.
18. Fiastro JF, Habib MP, Quan SF. Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. *Chest* 1988; 93: 499-505.
19. Klain M, Smith B. High frequency percutaneous trans-tracheal jet ventilation. *Critical Care Medicine* 1977; 5: 280-287.
20. Chang HK, Harf A. High frequency ventilation: a review. *Respiratory Physiology* 1984; 57: 135-152.
21. Isabey D, Harf A, Chang HK. Alveolar ventilation during high-frequency oscillation: core dead space concept. *Journal of Applied Physiology* 1984; 56: 700-707.
22. Poon C, Ward S, Whipp B. Influence of inspiratory assistance on ventilatory control during moderate exercise. *Journal of Applied Physiology* 1987; 62: 551-560.

COMMENTARY

GUEST REVIEWERS FOR 1991

Each manuscript submitted to *British Journal of Anaesthesia* is reviewed by members of the Editorial staff, and also by individuals with particular expertise in the area of study under consideration. All reviewers are asked to consider the scientific merit of each communication and its relevance to the clinical practice of anaesthesia. Consequently, acceptance for publication is based on the views of two or more individuals as to originality, validity and clinical relevance of the information presented.

The Editor would like to acknowledge the significant contributions made by the undernoted individuals who, in addition to the Editorial team, reviewed manuscripts during 1991.

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CORRESPONDENCE

VENOUS SEQUELAE AFTER I.V. DICLOFENAC

Sir,—I read the article "Venous sequelae following i.v. administration of diclofenac" in the *British Journal of Anaesthesia* [1]. As a further attempt to prevent thrombosis, diclofenac 75 mg was diluted in 100–200 ml of parenteral fluid which remained in the infusion bottle during surgery, and was administered over 15–20 min in 25 patients via a 22-gauge cannula on the dorsum of the hand other than that used for infusions.

Surprisingly, there was no local venous thrombosis in any of the patients on observation until 72 h. Although the number of patients studied was very small, it may be beneficial to infuse the drug where the i.v. route is chosen.

R. GOPINATH
Hyderabad

REFERENCE

1. Campbell WI, Watters CH. Venous sequelae following i.v. administration of diclofenac. *British Journal of Anaesthesia* 1989; 62: 545–547.

Sir,—Thank you for giving us the opportunity to reply to Dr Gopinath's letter regarding the use of i.v. diclofenac. His findings would indicate that further dilution of diclofenac may further reduce the incidence of venous thrombosis (his dilution is 5–10 fold that which we used).

He does not state which preparation of diclofenac was used, but I presume it was the i.m. preparation identical to that used in our study (diclofenac 75 mg in 3 ml).

Although we have found diclofenac valuable in the management of pain after some types of surgery [1], diclofenac is still not licensed for i.v. use in this country. This is unfortunate, as this drug has a relatively good safety profile and has considerable potential. Unfortunately, the i.m. route is painful and the onset of action slow.

W. CAMPBELL
C. WATTERS
Belfast

REFERENCE

1. Campbell WI, Kendrick R, Patterson C. Intravenous diclofenac sodium. Does its administration before operation suppress postoperative pain? *Anaesthesia* 1990; 45: 763–766.

INTRA-ARTERIAL REGIONAL ANALGESIA

Sir,—In their paper on intra-arterial regional analgesia of the hand [1], Koscielniak-Nielsen and Stens-Pedersen state that the Vishnevsky technique of "squirt and cut" local anaesthesia was used in the Crimean war.

This was not possible. The Allied armies landed in the Crimea on September 14, 1854. Carl Koller did not discover and describe the local anaesthetic properties of cocaine until almost exactly 30 years later, in September, 1884 [2].

May I add a note about Vishnevsky. It was my good fortune to meet and become friends with General Vishnevsky in Moscow 30 years ago. He was a skilled surgeon, Head Doctor at the Vishnevsky Clinic in Moscow, and son of the man after whom the technique was named. In the grounds of the institute is a huge marble statue of his father.

The "squirt and cut" method can be more scientifically described as follows: "Use 0.25 % lignocaine plain: you may use as much as is necessary; inject all sites before you incise them." It was a method still widely used in even the best Moscow clinics, for example the Borkin, in the late 1950s and early 1960s, combined, it must be said, with heavy sedation.

T. R. AUSTIN
Cardiff

REFERENCES

1. Koscielniak-Nielsen ZJ, Stens-Pedersen HL. Intra-arterial regional analgesia of the hand. *British Journal of Anaesthesia* 1991; 66: 719–720.
2. Koller C. Über die Verwendung des Cocain zur Anaesthesirung am Auge. *Weiner Medizinische Wochenschrift* 1884; 34: 1276.

Sir,—I wish to comment on some historical events referred to in the paper by Koscielniak and colleagues [1]. The first record of the injection of cocaine into arteries was with a view to determine its toxicity [2]. The method of intra-arterial regional analgesia was first described in animals and in humans by the vascular surgeon J. Goyanes (1876–1964) in 1908, not in 1912 [3].

He obtained much the same results with the injection of weak solutions of cocaine, eucaine and novocaine into arteries between two tourniquets as could be obtained with i.v. administration. The local anaesthetic is carried by the capillaries to the individual nerve-endings [4, 5].

In additional studies, Goyanes used intra-arterial regional analgesia with novocaine in 70 patients for surgical procedures of the extremities, with only two failures of the technique [6].

F. GILSANZ
Madrid

REFERENCES

1. Koscielniak-Nielsen ZJ, Stens-Pedersen HL. Intra-arterial regional analgesia of the hand. *British Journal of Anaesthesia* 1991; 66: 719–720.
2. Allen CW. Intra-arterial anaesthesia. In Allen CW, ed. *Local Anaesthesia*. Philadelphia: W. B. Saunders Company, 1920; 211–220.

3. Goyanes Capdevilla J. Un nuevo método de anestesia regional. *Revista Clínica de Madrid* 1908; 4: 12-19.
4. Goyanes Capdevilla J. La anestesia por vía arterial. *Revista Clínica de Madrid* 1912; 8: 401-422.
5. Goyanes Capdevilla J. La anestesia por vía arterial. *Revista de Medicina y Cirugía Prácticas* 1912; 108: 416-423.
6. Goyanes Capdevilla J. Algunos problemas interesantes de la narcosis, y especialmente la narcosis intravascular. *Revista Clínica de Madrid* 1913; 10: 327-343.

Sir,—Please do excuse the unfortunate error caused by our ignorance of the terminology used in British history textbooks. The "Crimean war" to which we refer took place during the Second World War, when the Red Army conquered the Crimean Peninsula. The "squirt and cut" method was widely used there by its surgeons (lectures on the history of wartime surgery delivered by the late Prof. Sylwanowicz for his students in Warsaw, Poland, in the 1970s). Our apologies to Dr Austin and all other colleagues misled by our imprecise statement.

I thank Dr Gilsanz for his valuable comments on the origin of intra-arterial analgesia. Despite an extensive search in the medical literature in both Europe and Canada, we could not trace the original articles dealing with the subject. Unfortunately, articles published in the Spanish medical journals at the beginning of the century are not included in the existing databases, nor is the chapter in Allen's book. Therefore, after lengthy correspondence with the editors, a compromise was reached to present the references as published.

Z. J. KOSCIELNIAK-NIELSEN
Montreal

TRACHEAL INTUBATION WITH THE PATIENT IN THE SITTING POSITION

Sir,—I wish to make the following observations on the letter of Brock-Utne and Jaffe [1]. The effectiveness of the head-up position in preventing regurgitation was demonstrated long ago [2], although it does not, of course, protect against active vomiting. One suspects that the reason it was not adopted widely was because the use of cricoid pressure was described soon after by Sellick [3], and this became an essential for safe practice.

I was fortunate when training at Frenchay Hospital, Bristol in the early 1950s to be taught by Dr Tom Wilton and Mr Ronald Belsey the technique of bronchoscopy under local analgesia with the patient seated in a dental chair; on many occasions since, when faced with a difficult or hazardous intubation, I have been grateful for this experience.

The technique of local analgesia is simpler than that described by Brock-Utne and Jaffe, involving spraying the pharynx, then anaesthetizing the glottis and bronchial tract under indirect vision using a laryngeal mirror and syringe to trickle lignocaine first onto the vocal cords and then through the larynx into the bronchial tract. This is the easiest and least uncomfortable method for the conscious patient. I have seldom needed to use invasive methods such as cricothyroid injection or laryngeal nerve block, except in the occasional uncooperative patient.

Both laryngoscopy and rigid bronchoscopy are easier with the patient sitting, partly because the head and neck can be moved into the appropriate position more readily than when the subject is lying flat. More importantly, the tongue and soft tissues fall away from the airway when in the vertical position, as exemplified by the fact that patients suffering from respiratory distress instinctively take up this posture to ease their breathing. One might suggest that the airway is even better protected if topical anaesthesia is taken only as far as the glottis, thus retaining the cough reflex in the trachea. With immediate cuff inflation, and rapidly acting i.v. agents, the effects of coughing as the tube is passed are minimized.

Whether standard or fiberoptic techniques are preferable I cannot judge, as I retired from clinical practice before mastering the latter!

A. K. ADAMS
Cambridge

REFERENCES

1. Brock-Utne JG, Jaffe RA. Tracheal intubation with the patient in the sitting position. *British Journal of Anaesthesia* 1991; 67: 225-226.
2. Snow RG, Nunn JF. Induction of anaesthesia in the foot-down position in patients with a full stomach. *British Journal of Anaesthesia* 1959; 31: 493-497.
3. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961; 2: 404-406.

BOOK REVIEW

Towards a New Pharmacotherapy of Pain. Edited by A. I. Basbaum and J.-M. Besson. Published (1991) by John Wiley & Sons Ltd. Pp. 457; indexed; illustrated. Price £65.00.

This book is the report of a Dählem workshop held in Berlin in 1989. There are four main sections. The first is on the physiological and pharmacological bases of nociceptive message control and transmission. The second is about opioid tolerance. The third section concerns the molecular basis of opioid antinociception and the use of this information for the design of new drugs. The fourth is about neuropathic pain after peripheral injury.

The calibre of the participants was extremely high, with a mix of European and American. The format is that individual papers relevant to the heading are followed by a group report on the topic. The standard of many of the papers is extremely high. Although some topics have necessarily been marginally overtaken by events in the 2 years since the meeting, the choice of topics was sufficiently perceptive that most remain leading-edge summaries of problem areas in both basic and clinical pain work. The cross-disciplinary format results in thought-provoking conclusions.

The clinical aspects are most evident in the tolerance and neuropathic pain sections. Tolerance remains enigmatic; in acute settings it is rarely a clinical problem, and similarly in chronic pain management we usually interpret increased drug requirement to indicate increase in pain intensity or change in the character (and hence analgesic sensitivity) of the pain. We have no real understanding of why patients can still obtain effective analgesia with few, or manageable, side effects. We assume that this is a result of the dose-response curve for analgesia being left-shifted relative to that for the side effects, and perhaps the shape of the curves is also different. The

clinical chapter in the tolerance section explores the influence of previous opioid exposure. It includes data from Dr Houde at Memorial Sloan-Kettering. He and his colleagues did unique controlled studies in many areas of analgesic research, but published them in obscure reports, so that the information takes many years to percolate through. The data shown here indicate that the analgesic dose-response curve for morphine is shifted to the right when the effect of two doses is separated by 14 days. The basic science chapters show that the mechanisms of tolerance include a rapid (hours) desensitization specific to receptor subtype and a slower process of down-regulation, again specific to receptor subtype, but with an estimated maximum extent of 30–40%. In most anaesthetic contexts the desensitization would appear to be the more important mechanism. The chapters also emphasize the importance of the degree of receptor occupancy. Opioids with a high degree of efficacy at a particular subtype need to occupy only a small fraction of the receptors to achieve the desired effect compared with opioids of lesser efficacy. Tolerance development will be more marked with drugs of lesser efficacy. It is this difference in occupancy which is the probable explanation of incomplete cross-tolerance.

The treatment of neuropathic pain is a major problem for anaesthetists involved in chronic pain. The chapters reflect the various controversies, the heterogeneity of the pathogenesis, the involvement of the sympathetic nervous system and the sensitivity of neuropathic pain to conventional analgesics. There are interesting thoughts which would not emerge in journal articles, but nothing new clinically.

I think that this is a stimulating book. It reads as though the meeting was stimulating. It is not light reading, and is a book for the specialist. It is well put together.

H. J. McQuay

AUTHOR INDEX

VOLUME 67, 1991

British Journal of Anaesthesia

ARS = Anaesthetic Research Society papers

C = Correspondence

E = Editorial

R = Book review

- AANTAA, R., JAAKOLA, M.-L., KALLIO, A., KANTO, J., SCHEININ, M. and VUORINEN, J. A comparison of dexmedetomidine, an α_2 -adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery 402-409
- ABDULATIF, M. *see* NAGUIB, M. 320-322
- ABSOOD, A. *see* NAGUIB, M. 320-322
- ADAMS, A. K. Tracheal intubation with the patient in the sitting position, (C) 804
- ADAMS, A. P. *see* KING, T. A., (C) 225
- ADNET, P. *see* KRIVOSIC-HORBER, R., (C) 221
- AITKEN, H. A., TODD, J. G. and KENNY, G. N. C. Comparison of the Finapres and direct arterial pressure monitoring during profound hypotensive anaesthesia 36-40
- AITKEN, H. A. *see* BURNS, J. W. 235-238
- AITKENHEAD, A. R. *see* LIU, D. W. H., (ARS) 208-209P; LIU, W. H. D. 768-771
- AKHTAR, T. M., KERR, W. J. and KENNY, G. N. C. Comparison of laryngeal mask airway with tracheal intubation for intraocular surgery, (ARS) 215P
- AKHTAR, T. M., RIDLEY, S. and BEST, C. J. Unusual presentation of acute upper airway obstruction caused by an anterior mediastinal mass 632-634
- ALAHUHTA, S., RÄSÄNEN, J., JOUPPIA, R., JOUPPIA, P. and HOLLMÉN, A. I. Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation 678-682
- AL-MUHANDIS, W. M., LAURETTI, G. R. and PLEUVRY, B. J. Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanum and strychnine 608-613
- AL-SHAIKH, B. Desaturation during total knee replacement, (C) 502
- AMAR, D., SHAMOON, H., FRISHMAN, W. H., LAZAR, E. J. and SALAMA, M. D. Effects of labetalol on perioperative stress markers and isoflurane requirements 296-301
- AMOROSO, P., WILSON, S. R., PONTÉ, J. C., GINSBURG, R. and MOXHAM, J. Effect of inhaled salbutamol on resting oxygen consumption, (ARS) 210P
- AMOROSO, P. *see* WILSON, S. R., (ARS) 216-217P
- ANDERTON, J. M. The prone position for the surgical patient: a historical review of the principles and hazards 452-463
- ANDREWS, P. J. D., DEARDEN, N. M. and MILLER, J. D. Comparison of thiopentone and propofol at two rates of administration in patients with severe head injury, (ARS) 212P; Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor 553-558
- ANKER-MØLLER, E. *see* ARENDT-NIELSEN, L., (C) 227
- APFELBAUM, J. L. *see* LICHTOR, J. L. 579-584
- ARENDT-NIELSEN, L. and ANKER-MØLLER, E. Analgesia with subhypnotic doses of thiopentone and propofol, (C) 227
- ARGIRAS, E. *see* PALAZZO, M. G. A. 759-763
- ARIEFF, A. I. Indications for use of bicarbonate in patients with metabolic acidosis 165-177
- ARINO, P. *see* CRONEN, M. C. 480-482
- ARMSTRONG, C. *see* PATTERSON, K. W., (ARS) 213-214P
- ARMSTRONG, P. J., MORRISON, L. M., NOBLE, D., SINCLAIR, W. A., TIPLADY, B. and WILDSMITH, J. A. W. Effects of i.v. lignocaine on psychological performance and subjective state in healthy volunteers 532-538
- ARNDT, J. O. *see* KLEMENT, W. 281-284; (C) 507
- ASBURY, A. J. Systolic arterial pressure as a monitor of depth of anaesthesia, (C) 506
- ASBURY, A. J. *see* O'DONNELL, C. A., (ARS) 658-659P; O'DONNELL, N. G., (ARS) 661P
- ASHTON, W. B., JAMES, M. F. M., JANICKI, P. and UYS, P. C. Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section 741-747
- AUKBURG, S. J. *see* TOBIAS, M. D. 332-334
- AUSTIN, T. R. Intra-arterial regional analgesia, (C) 803
- BADER, A. M. *see* CAMANN, W. R. 565-568
- BALDWIN, A. M. *see* KLUGER, M. T., (ARS) 656-657P
- BALL, C. *see* WILSON, S. R., (ARS) 216-217P
- BALLESTEROS, M. *see* BOLDT, J. 595-602
- BANNISTER, P. *see* CARLI, F. 729-734
- BARASH, P. G. *see* STOELTING, R. K., (R) 229
- BARKAI, A. I. *see* YOUNG, W. L. 440-446
- BARKER, P., MURPHY, P., LANGTON, J. A. and ROWBOTHAM, D. J. Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, (ARS) 660P
- BARKER, P. *see* LANGTON, J., (ARS) 648-649P; MURPHY, P. J., (ARS) 660-661P
- BARNARD, M. *see* WEBSTER, J. 467-469
- BARNES, P. J. *see* CRYSTAL, R. G., (R) 230
- BARSON, W. G., JASTREMSKI, M. S. and SYVERUD, S. A., (editors) *Emergency Drug Therapy*, 1st Edn, (R) 508-509
- BARTLETT, S. *see* CARLI, F. 729-734
- BASBAUM, A. I. and BESSON, J.-M., (editors) *Towards a New Pharmacotherapy of Pain*, (R) 805
- BAXTER, M. J. *see* NOLAN, K. M., (ARS) 650-651P
- BEALE, R. J. *see* FAIRFIELD, J. E. 618-620
- BECKER, P. *see* VAN HEERDEN, P. V. 470-472
- BEECH, M. J. *see* POMFRETT, C. J. D., (ARS) 646-647P
- BEEMER, G. H. and BJORKSTEN, A. R. Determinants of antagonism of non-depolarizing neuromuscular block, (C) 362
- BEEMER, G. H., BJORKSTEN, A. R. and CRANKSHAW, D. P. Pharmacokinetics of atracurium, (C) 129-130
- BELL, D. *see* MCCLOY, R., (C) 504
- BELL, J. *see* EVANS, R. D., (ARS) 217P
- BELLHOUSE, P. Predicting difficult intubation, (C) 505; Unexpected, difficult laryngoscopy, (C) 501
- BEN-DAVID, B. *see* LEE, E., (C) 130

- BERRISFORD, R. G. *see* ENTWISTLE, M. D. 704-711
- BERRY, A. *see* SNEYD, J. R., (ARS) 659-660P
- BERTAN, V. *see* TEKOK, I. H. 112-115
- BERTHOUD, M. C., PEACOCK, J. E. and REILLY, C. S.
Comparison of infusion rates of thiopentone for
induction of anaesthesia in elderly patients, (ARS)
645P; Effectiveness of preoxygenation in morbidly
obese patients 464-466
- BESSON, J.-M. *see* BASBAUM, A. I., (R) 805
- BEST, C. J. *see* AKHTAR, T. M. 632-634
- BEYDON, L., ISABEY, D., BOUSSIGNAC, G., BONNET, F.,
DUVALDESTIN, P. and HARR, A. Pressure support
ventilation using a new tracheal gas injection tube
795-800
- BISNAIRE, D. *see* DAVIES, K. R. 58-63
- BISSONNETTE, B. *see* YENTIS, S. M. 779-780
- BJORKSTEN, A. R. *see* BEEMER, G. H., (C) 129-130; (C) 362
- BLACK, A. M. S. and KOEHLI, N. Post-Post-Tetanic
Facilitation Fade (PPTFF), (ARS) 220P
- BLAKE, G. J. P. *see* YOUNG, J. D., (ARS) 209P
- BLOGG, C. E. *see* URB, R. W., (ARS) 657-658P
- BOER, F., BOVILL, J. G., ROS, P. and VAN OMMEN, H.
Effect of thiopentone, etomidate and propofol on
systemic vascular resistance during cardiopulmonary
bypass 69-72
- BOGLE, R. G. *see* PETROS, A. J., (ARS) 645-646P
- BOLDT, J., ZICKMANN, B., HEROLD, C., BALLESTEROS, M.,
DAPPER, F. and HEMPELMANN, G. Influence of
hypertonic volume replacement on the microcirculation
in cardiac surgery 595-602
- BOLSIN, S. *see* RAFTERY, S., (ARS) 651-652P
- BOLTE, M. *see* KIEZMANN, D. 269-276
- BONNET, F. *see* BEYDON, L. 795-800; DELAUNAY, L.
397-401
- DE BONO, D. P. and ROSE, E. L. Silent myocardial
ischaemia in preoperative patients: what does it mean,
and what should be done about it? (E) 367-368
- BOOKER, P. D. *see* WENSTONE, R. 591-594
- BORGEAT, A. *see* WILDER-SMITH, O., (C) 226-227
- BOUCHIER-HAYES, D. *see* RYAN, T., (ARS) 204-205P
- BOUGHNER, D. R. *see* DAVIES, K. R. 58-63
- BOUSSIGNAC, G. *see* BEYDON, L. 795-800
- BOVILL, J. G. *see* BOER, F. 69-72
- BOYS, R. J. *see* COLEMAN, S. A. 257-261
- BRACEY, B. J. *see* GOLDHILL, D. R. 289-295
- BRAUDE, N., VYVYAN, H. A. L. and JORDAN, M. J.
Intraoperative assessment of atracurium-induced
neuromuscular block using double burst stimulation
574-578
- BRECKON, D. A. *see* JESSOP, J. 524-531
- BRIMACOMBE, J. Training in fiberoptic laryngoscopy, (C)
503
- BRISTOW, A. Transfer of patients by helicopter, (C) 127
- BROCK-UTNE, J. G. and JAFFE, R. A. Tracheal intubation
with the patient in a sitting position, (C) 225-226
- BROOKES, S. T. *see* DEVLIN, J. C., (ARS) 651P
- BROOME, I. J., HARRIS, R. and REILLY, C. S. Response time
of finger and ear pulse oximeter probes during
hypoxaemic events occurring during anaesthesia,
(ARS) 207P
- BROWN, D. T. *see* READ, J. R. M., (ARS) 216P
- BROWN, R. A. and SWANSON BECK, J. *Medical Statistics on
Microcomputers*, 1st Edn, (R) 132-133
- BROWN, R. W. and HEATH, M. L. Resuscitation training for
the operating department, (ARS) 219-220P
- BROWNE, B. *see* RAFTERY, S., (ARS) 218P
- BROWNE, G. P. R., LEA, K., WOOD, P. and KOX, W. J.
Haemodynamic and oxygen transport effects of
isoflurane as sedation in ventilated patients in the
intensive care unit, (ARS) 652P
- BROWNDRIDGE, P. Spinal anaesthesia in obstetrics, (C) 663
- DEBRUIJN, N. P. and CLEMENTS, F. M., (editors)
Intraoperative Use of Echocardiography (A Society of
Cardiovascular Anesthesiologists Monograph), (R)
668-669
- BUCHAN, A. S. and SHARWOOD-SMITH, G. H. *Handbook of
Obstetric Anaesthesia*, (R) 509
- BULLINGHAM, R. E. S. *see* BURNS, J. W. 235-238
- BURNS, J. W., AITKEN, H. A., BULLINGHAM, R. E. S.,
MCARDLE, C. S. and KENNY, G. N. C. Double-blind
comparison of the morphine sparing effect of
continuous and intermittent i.m. administration of
ketorolac 235-238
- BURRIN, J. M. *see* DESBOROUGH, J. P. 390-396
- CALVO, M. B. *see* PEDRAZ, J. L. 310-316
- CAMANN, W. R., HORTVET, L. A., HUGHES, N., BADER,
A. M. and DATTA, S. Maternal temperature regulation
during extradural analgesia for labour 565-568
- CAMPANELLA, C. *see* WORSLLEY, M. H. 116-119
- CAMPBELL, I. T. *see* DEVLIN, J. C., (ARS) 651P
- CAMPBELL, J. M. *see* WENSTONE, R. 591-594
- CAMPBELL, J. R. Determinants of antagonism of non-
depolarizing neuromuscular block, (C) 362
- CAMPBELL, W. and WATERS, C. Venous sequelae after i.v.
diclofenac, (C) 803
- CARABINE, U. A., MILLIGAN, K. R. and MOORE, J.
Preanaesthetic medication: comparison of three drug
groups, (ARS) 659P
- CARABINE, U. A., WRIGHT, P. M. C. and MOORE, J.
Preanaesthetic medication with clonidine: a
dose-response study 79-83
- CARLI, F., WEBSTER, J., PEARSON, M., PEARSON, J.,
BARTLETT, S., BANNISTER, P. and HALLIDAY, D. Protein
metabolism after abdominal surgery: effect of 24-h
extradural block with local anaesthetic 729-734
- CARLI, F. *see* CORMACK, R. R., (C) 501-502; WEBSTER, J.
467-469
- CARP, H. *see* MILLIGAN, H. R., (C) 131
- CARRIE, L. E. S. First use of combined spinal-extradural
anaesthesia, (C) 667
- CARTER, M. *see* SMITH, C. 262-268
- CASEY, K. R. *see* REEDER, M. K. 326-328
- CASEY, P. B. *see* PATTERSON, K. W. 108-111
- CASHMAN, J. N. *see* FENNER, S. G. 483-487; (C) 665
- CASOLARO, V. *see* STELLATO, C. 751-758
- CATALTEPE, O. *see* TEKOK, I. H. 112-115
- CHAKRABARTI, M. K. *see* HACKMAN, C. H. 346-352
- CHAN, K. *see* GIN, T. 49-53
- CHARLESWORTH, C. H. *see* MARSH, A. M. 517-523
- CHARTERS, P. *see* MARKS, R. R. D., (ARS) 654P
- CHEKNACK, N. S. *see* CRYSTAL, R. G., (R) 230
- CHONDRELI, S. *see* FASSOULAKI, A. 437-439
- CHUI, P. T. *see* SHORT, T. G. 539-545
- CHUNG, R. and SONI, N. C. Work of ventilating heat and
moisture exchangers, (ARS) 647-648P
- CHUNG, R. A. and GOODWIN, A. M. Transient ischaemic
attack after spinal anaesthesia 635-637
- CHURCH, J. Opioid receptors—the role of the sigma
receptor? (C) 361-362
- CICCARELLI, A. *see* STELLATO, C. 751-758
- CLARKE, R. S. J. *see* MCCLUNE, S., (ARS) 215-216P;
McLOUGHLIN, C. 764-767
- CLEMENTS, F. M. *see* DEBRUIJN, N. P., (R) 668-669
- CLUTTON-BROCK, T. *see* STOKES, D. N. 26-35
- COCKS, D. A. *see* LAURENCE, A. S., (ARS) 202-203P
- COHEN, R. D. Roles of the liver and kidney in acid-base
regulation and its disorders 154-164
- COLD, G. E. *see* KNUDSEN, L. 277-280
- COLE, J. *see* WATSON, D., (ARS) 656P
- COLEMAN, S. A., MCCRORY, J. W., VALLIS, C. J. and BOYS,
R. J. Inhalation induction of anaesthesia with
isoflurane: effect of added carbon dioxide 257-261

- COLUMB, M. O. Inappropriate heparinization with a cell saver, (C) 223
- COLVIN, J. R. *see* SKIPSEY, I. G., (ARS) 218-219P
- CONACHER, I. D. *see* SHAW, I. H. 772-778
- COOK, L. B. Unsuspected extradural catheterization in an interscalene block 473-475
- COOLEY, J. M. *see* SEVERN, A. M., (ARS) 650P
- COONEY, C. and GALLAGHER, H. Spinal needles, (C) 360-361
- COOPER, P. and MEDDINGS, J. B. Malignant hyperthermia: a generalized abnormality of membrane fluidity? (ARS) 201-202P
- COOPER, R. *see* MCCARTHY, G., (ARS) 652-653P
- CORMACK, R. R., CARLI, F. and WILLIAMS, K. N. Unexpected, difficult laryngoscopy, (C) 501-502
- COUTO DA SILVA, J. M. Systolic arterial pressure as a monitor of depth of anaesthesia, (C) 506
- CRANKSHAW, D. P. *see* BEEMER, G. H., (C) 129-130
- CRONEN, M. C., CRONEN, P. W., ARINO, P. and ELLIS, K. Delayed pneumothorax after subclavian vein catheterization and positive pressure ventilation 480-482
- CRONEN, P. W. *see* CRONEN, M. C. 480-482
- CRYSTAL, R. G., WEST, J. B., BARNES, P. J., CHERNIACK, N. S. and WEIBAL, E. R., (editors) *The Lung—Scientific Foundations*, (R) 230
- CUNNINGHAM, A. J. *see* PATTERSON, K. W. 108-111; RYAN, T., (ARS) 204-205P
- CYNA, A. M., KULKARNI, V., TUNSTALL, M. E., HUTCHISON, J. M. S. and MALLARD, J. R. AURA: a new respiratory monitor and apnoea alarm for spontaneously breathing patients 341-345
- DANSKIN, F. H. *see* McLINTIC, A. J. 683-689
- DAPPER, F. *see* BOLDT, J. 595-602
- DAROWSKI, M. J. *see* KUSHIMO, O. T. 781-783
- DATTA, S. *see* CAMANN, W. R. 565-568
- DAVIES, K. R., GELB, A. W., MANNINEN, P. H., BOUGHNER, D. R. and BISNAIRE, D. Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities 58-63
- DAVIES, M. J. *see* MURPHY, P. G., (ARS) 649-650P
- DAVIS, C. L. Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, (C) 362-363
- DAVIS, P. D. *see* PARBROOK, G. D., (R) 230
- DAWLATLY, A. A. *see* NAGUIB, M. 559-564
- DEARDEN, N. M. *see* ANDREWS, P. J. D., (ARS) 212P; 553-558
- DEBEY, R. K. *see* HEINING, M. P. D. 120-126
- DELAUNAY, L., BONNET, F. and DUVALDESTIN, P. Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia 397-401
- DEMELLO, W. F. Transfer of patients by helicopter, (C) 127
- DENNISON, A. R. *see* WATSON, D., (ARS) 656P
- DESBOROUGH, J. P., HALL, G. M., HART, G. R. and BURRIN, J. M. Midazolam modifies pancreatic and anterior pituitary hormone secretion during upper abdominal surgery 390-396
- DEVLIN, J. C., BROOKES, S. T., SAMUELS, T., GREEN, C. and CAMPBELL, I. T. Measurement of energy expenditure in critical illness using ^{13}C labelled bicarbonate, (ARS) 651P
- DODSON, M. E. Picolax bowel preparation, (C) 664
- DOHRN, C. *see* LICHTOR, J. L. 579-584
- DOMINGUEZ-GIL, A. *see* PEDRAZ, J. L. 310-316
- DONATI, F. Atracurium and suxamethonium, (C) 502
- DORAN, B. R. H. *see* SNEYD, J. R., (ARS) 647P
- DORRINGTON, K. L. *see* RATCLIFFE, F. M., (ARS) 203-204P; YOUNG, J. D., (ARS) 209P
- DRITSAS, A. *see* FAIRFIELD, J. E. 618-620
- DRUMMOND, G. B., MCGOWAN, S. and DUFFY, N. D. A rapid method to assess chest wall shape and volume change, (ARS) 204P
- DRUMMOND, G. B. *see* MARAN, N. J., (ARS) 648P; RAY, D. C. 84-99; READ, J. R. M., (ARS) 216P; RUTHERFORD, J. S., (ARS) 647P; SWANN, D. G., (ARS) 644P
- DUFFY, N. D. *see* DRUMMOND, G. B., (ARS) 204P
- DUNDEE, J. W. and MAHDI, A. A. L. Relationship of postoperative and cancer chemotherapy sickness, (ARS) 214P
- DUNNET, J. M., HOLLAND, D. E. and PRYS-ROBERTS, C. Dose requirements to suppress consciousness by continuous infusion of propofol in young adults, (ARS) 214-215P
- DURKIN, M. *see* YOUNG, W. L. 440-446
- DUVALDESTIN, P. *see* BEYDON, L. 795-800; DELAUNAY, L. 397-401
- DWYER, S. J. *see* URE, R. W., (ARS) 657-658P
- EDMONDSON, C. *see* McLAUCHLAN, G. A., (ARS) 211P
- EDWARDS, D. *see* SNEYD, J. R., (ARS) 647P
- ELDOR, J. First use of combined spinal-extradural anaesthesia, (C) 666
- EL GAMMAL, M. *see* NAGUIB, M. 559-564
- ELLIOTT, P. *see* MCCARTHY, G., (ARS) 652-653P
- ELLIOTT, R. H. *see* SANDHAR, B. K., (ARS) 213P
- ELLIS, F. R. *see* HOPKINS, P. M., (ARS) 202P
- ELLIS, K. *see* CRONEN, M. C. 480-482
- EMMOTT, R. S. *see* GOLDHILL, D. R. 289-295
- ENEVER, G., RAFTERY, S. and PRYS-ROBERTS, C. Hyperventilation and blood concentrations of propofol during total i.v. anaesthesia, (ARS) 217-218P
- ENEVER, G. *see* RAFTERY, S., (ARS) 218P
- ENTWISTLE, M. D., ROE, P. G., SAPSFORD, D. J., BERRISFORD, R. G. and JONES, J. G. Patterns of oxygenation after thoracotomy 704-711
- ERDMANN, E. and REUSCHEL-JANETSCHKE, E. Calcium for resuscitation? 178-184
- EVANS, R. D., PATEL, S., SEAR, J. W., BELL, J., LODGE, J., HAHN, C. E. W. and SADLER, P. J. Anaesthetic-plasma interactions: a study using nuclear magnetic resonance spectroscopy (MRS), (ARS) 217P
- EVANS, W. D. *see* YEE, M. K. 426-431
- FACEY, P. E. *see* YEE, M. K. 426-431
- FAIRFIELD, J. E., DRITSAS, A. and BEALE, R. J. Haemodynamic effects of propofol: induction with 2.5 mg kg^{-1} 618-620
- FARQUHAR, I. K. *see* WATSON, D., (ARS) 656P
- FASSOULAKI, A., SARANTOPOULOS, C. and CHONDRELI, S. Systemic fentanyl enhances the spread of spinal analgesia produced by lignocaine 437-439
- FAULDER, G. C. *see* MAZUMBAR, B. 432-436
- FAUVEL, N. J. and FELDMAN, S. A. Atracurium and suxamethonium, (C) 502
- FAUVEL, N. J. *see* FELDMAN, S. A., (ARS) 206P; GUPTA, V. L., (ARS) 211P
- FEIGENWINTER, P. *see* ZBINDEN, A. M. 492-499
- FELDMAN, S. A. and FAUVEL, N. J. Potentiation and antagonism of vecuronium by decamethonium in man, (ARS) 206P
- FELDMAN, S. A. *see* FAUVEL, N. J., (C) 502; GUPTA, V. L., (ARS) 211P
- FENNER, S. G. and CASHMAN, J. N. Anaesthesia and bone marrow aplasia, (C) 665
- FENNER, S. G., MAHONEY, A. and CASHMAN, J. N. Repair

- of traumatic transection of the thoracic aorta: esmolol for intraoperative control of arterial pressure 483-487
- FERNANDO, R. and JONES, H. M. Comparison of plain and alkalized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural Caesarean section 699-703
- FIEBIG, M. *see* LYNCH, J. 690-693
- FINFER, S. R. Interference with pacemaker function, (C) 664-665: Management of labour and delivery in patients with intracranial neoplasms 784-787
- FLETCHER, R. *see* MALMROS, C., (ARS) 655P
- FLYNN, P. J. *see* GOLDHILL, D. R. 289-295
- FOËX, P. *see* JEWKES, C. 788-794; MUIR, A. D. 373-377; REEDER, M. K. 626-631
- FRISHMAN, W. H. *see* AMAR, D. 296-301
- FROST, E. A. M. and GOLDINER, P. L., (editors) *Postanaesthetic Care*, (R) 133
- FUJIMORI, R. *see* NAITO, Y. 387-389
- FURNESS, P. *see* JESSOP, J. 524-531
- GALLAGHER, H. *see* COONEY, C., (C) 360-361
- GALLAGHER, T. J. *see* STOLTING, R. K., (R) 229
- GALLETLY, D. C. *see* PARR, S. M. 447-451
- GANDOLFI, A. J. *see* HASTINGS, K. L. 722-728
- GASCON, A. R. *see* PEDRAZ, J. L. 310-316
- GELB, A. W. *see* DAVIES, K. R. 58-63
- GELLER, E. *see* MCCLOY, R., (C) 504
- GENT, J. P. *see* GOODCHILD, C. S., (ARS) 201P
- GILL, N., WRIGHT, B. and REILLY, C. S. Relationship between perioperative ischaemic and hypoxic events in patients with cardiovascular disease, (ARS) 649P
- GILMAN, A. G., RALL, T. W., NIBS, A. S. and TAYLOR, P., (editors) *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 8th Edn, (R) 133
- GILSANZ, F. Intra-arterial regional analgesia, (C) 803-804
- GIN, T., YAU, G., JONG, W., TAN, P., LEUNG, R. K. W. and CHAN, K. Disposition of propofol at Caesarean section and in the postpartum period 49-53
- GINSBURG, R. *see* AMOROSO, P., (ARS) 210P
- GO, G. *see* SHARROCK, N. E. 694-698
- GOLDHILL, D. R., WHITEHEAD, J. P., EMMOTT, R. S., GRIFFITH, A. P., BRACEY, B. J. and FLYNN, P. J. Neuromuscular and clinical effects of mivacurium chloride in healthy adult patients during nitrous oxide-enflurane anaesthesia 289-295
- GOLDHILL, D. R. *see* NOLAN, K. M., (ARS) 650-651P
- GOLDINER, P. L. *see* FROST, E. A. M., (R) 133
- GOLDMAN, M. D. *see* REEDER, M. K. 326-328; 626-631
- GOODCHILD, C. S., GUO, Z. and GENT, J. P. Spinally mediated antinociceptive effects of xylazine, an alpha-2 adrenoceptor agonist: interaction with spinal cord opioid pathways, (ARS) 201P
- GOODIE, D. B. and RIGG, D. L. Controlled hypotension for cerebral aneurysm surgery in the presence of severe aortic coarctation 329-331
- GOODWIN, A. M. *see* CHUNG, R. A. 635-637
- GOPINATH, R. Venous sequelae after i.v. diclofenac, (C) 803
- GOTO, R. *see* MIKAWA, K. 410-415; 416-420
- GRACE, A. *see* WHEATLEY, R. G., (ARS) 208P
- GRANDE, C. *see* STERNE, J. K., (R) 508
- GRAVENSTEIN, J. S. *Gas Monitoring and Pulse Oximetry*, (R) 230
- GREEN, C. *see* DEVLIN, J. C., (ARS) 651P
- GRICE, G. A. G. *see* MARKS, R. R. D., (ARS) 654P
- GRIFFITH, A. P. *see* GOLDHILL, D. R. 289-295
- GRIFFITHS, D. *see* NORTHWOOD, D. 7-12
- GRIFFITHS, D. E. *see* JESSOP, J. 524-531
- GRONERT, G. A. Myotonias and susceptibility to malignant hyperthermia, (C) 221
- GROVE, A. J. *see* MACPHERSON, R. D. 546-552
- GUO, Z. *see* GOODCHILD, C. S., (ARS) 201P
- GUPTA, V. L., FAUVEL, N. J. and FELDMAN, S. A. Investigation of fade in suxamethonium-induced phase II block in the isolated rat diaphragm, (ARS) 211P
- GWYNNUIT, C. L., WALKER, R. W. M. and MEAKIN, G. Antagonism of intense atracurium-induced neuromuscular block in children 13-16
- HACKL, W., WINKLER, M. and MAURITZ, W. Relationship between exercise-induced myolysis and malignant hyperthermia, (C) 221
- HACKMAN, C. H., TAN, P. S. K., CHAKRABARTI, M. K. and WHITWAM, J. G. A new optical transducer for arterial pressure measurement 346-352
- HAHN, C. E. W. *see* EVANS, R. D., (ARS) 217P
- HAHN, R. G. Dilutional hyponatraemia following transurethral operation for clot retention 339-340
- HALL, G. M. *see* DESBOROUGH, J. P. 390-396
- HALLIDAY, D. *see* CARLI, F. 729-734
- HALSALL, P. J. *see* HOPKINS, P. M., (ARS) 202P
- HAMILTON, W. K. Anaesthesia and bone marrow aplasia, (C) 665
- HANNA, M. H. Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, (C) 363
- HANSON III, C. W. *see* TOBIAS, M. D. 332-334
- HARF, A. *see* BEYDON, L. 795-800
- HARPER, N. J. N. *see* VOHRA, A. 64-68
- HARRIS, R. *see* BROOME, I. J., (ARS) 207P
- HART, G. R. *see* DESBOROUGH, J. P. 390-396
- HASEGAWA, M. *see* MIKAWA, K. 416-420
- HASTINGS, K. L., THOMAS, C., HUBBARD, A. K. and GANDOLFI, A. J. Screening for antibodies associated with halothane hepatitis 722-728
- HAYWARD, M. W. J. *see* YEE, M. K. 426-431
- HEAD-RAPSON, A. G., RALSTON, S. J. and SNOWDON, S. L. Desaturation and induction characteristics: comparison of propofol and thiopentone during mask anaesthesia with isoflurane, (ARS) 203P
- HEALY, T. E. J. *see* POMFRET, C. J. D., (ARS) 646-647P; SNEYD, J. R., (ARS) 647P; (ARS) 658P
- HEATH, M. L. *see* BROWN, R. W., (ARS) 219-220P
- VAN HEERDEN, P. V., MORRELL, D. F. and BECKER, P. Rapid inhalation induction with isoflurane in humidified carrier gas 470-472
- HEINING, M. P. D., DEBEY, R. K., MCJAMES, S. W., JORDAN, W. S. and WESTENSKOW, D. R. A system for automatic feedback control of plasma potassium concentration 120-126
- HEMPFELMANN, G. *see* BOLDT, J. 595-602
- HEPPENSTALL, R. B. *see* TOBIAS, M. D. 332-334
- HERNANDEZ, R. *see* PEDRAZ, J. L. 310-316
- HEROLD, C. *see* BOLDT, J. 595-602
- HIRSCH, N. *see* STEPHENS, P. H. 476-479
- HOLDGÅRD, H. O. *see* KNUDSEN, L. 277-280
- HOLLAND, D. E. *see* DUNNET, J. M., (ARS) 214-215P
- HOLLIS, S. *see* KUSHIMO, O. T. 781-783
- HOLLMÉN, A. I. *see* ALAHUHTA, S. 678-682
- HOPKINS, P. M., ELLIS, F. R. and HALSALL, P. J. *In vitro* contracture with the calcium ionophore A23187 in skeletal muscle from malignant hyperthermia susceptible and normal individuals, (ARS) 202P
- HORTVET, L. A. *see* CAMANN, W. R. 565-568
- HOUGHTON, I. T. *see* YOGANATHAN, S. 614-617
- HOWE, J. C. *see* OATES, J. D. L., (C) 505
- HUBBARD, A. K. *see* HASTINGS, K. L. 722-728
- HUGHES, N. *see* CAMANN, W. R. 565-568
- HUNTER, D. *see* WHEATLEY, R. G., (ARS) 208P; 353-359
- HUNTER, J. M. Resistance to non-depolarizing neuromuscular blocking agents, (E) 511-514
- HUNTER, J. M. *see* PARKER, C. J. R., (C) 129; PHILLIPS, B. J., (ARS) 653-654P; SHEARER, E. S. 569-573
- HUNTER, S. J. *see* SPITTAL, M. J. 488-491
- HUTCHISON, J. M. S. *see* CYN, A. M. 341-345

- HUTMACHER, M. *see* ZBINDEN, A. M. 492-499
 HUTTON, P. *see* STOKES, D. N. 26-35
- IAIZZO, P. *see* LEHMANN-HORN, F., (C) 221-222
 IEVINS, F. A. Regional anaesthesia requires attention to detail, (C) 225
 ILSLEY, A. H. *see* KLUGER, M. T., (ARS) 656-657P
 INGLIS, M. D. *see* McLEOD, G. A., (C) 665-666
 ISAAC, P. *see* SANDERS, L., (C) 504
 ISABEY, D. *see* BEYDON, L. 795-800
- JAAKOLA, M.-L. *see* AANTAA, R. 402-409
 JACKSON, I. J. B. *see* WHEATLEY, R. G. 353-359
 JACKSON, P. W. *see* SEVERN, A. M., (ARS) 650P
 JAFFE, R. A. *see* BROCK-UTNE, J. G., (C) 225-226
 JAMES, M. F. M. *see* ASHTON, W. B. 741-747
 JAMES, E. F. and McCORRY, J. W. The loading dose in continuous infusion extradural analgesia in obstetrics 323-325
 JANICKI, P. *see* ASHTON, W. B. 741-747
 JANSHON, G. *see* LEUWER, M., (ARS) 206-207P
 JASTREMSKI, M. S. *see* BARBAN, W. G., (R) 508-509
 JENSEN, S. *see* KNUDSEN, L. 277-280
 JESSOP, J., GRIFFITHS, D. E., FURNESS, P., JONES, J. G., SAPPFORD, D. J. and BRECKON, D. A. Changes in amplitude and latency of the P300 component of the auditory evoked potential with sedative and anaesthetic concentrations of nitrous oxide 524-531
 JEWKES, C., SEAR, J. W., VERHOEFF, F., SANDERS, D. J. and FOËX, P. Non-invasive measurement of cardiac output by thoracic electrical bioimpedance: a study of reproducibility and comparison with thermodilution 788-794
 JOEL, P. Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, (C) 363
 JOHANSEN, U. T. *see* KNUDSEN, L. 277-280
 JOHNSON, C. *see* TURNER, G. A. 306-309
 JOHNSTON, C. *see* MUIR, A. D. 373-377
 JOHNSTON, I. G. *see* YOGANATHAN, S. 614-617
 JONES, H. M. *see* FERNANDO, R. 699-703
 JONES, J. G. *see* ENTWISTLE, M. D. 704-711; JESSOP, J. 524-531; MURPHY, P. G., (ARS) 209-210P; (ARS) 649-650P; NORTHWOOD, D. 7-12
 JONES, L. *see* SPITAL, M. J. 488-491
 JONES, R. M. *see* TATMAN, A. J. 623-625
 JONES, S. N. *see* TINKER, J., (R) 669
 JONG, W. *see* GIN, T. 49-53
 JORDAN, M. J. *see* BRAUDE, N. 574-578
 JORDAN, W. S. *see* HEINING, M. P. D. 120-126
 JØRGENSEN, L. N. Deep venous thrombosis and anaesthesia, (C) 128
 JOSHI, P. *see* OOI, R., (ARS) 208P
 JOUPPILA, P. *see* ALAHUHTA, S. 678-682
 JOUPPILA, R. *see* ALAHUHTA, S. 678-682
- KAETSU, H. *see* MIKAWA, K. 410-415; 416-420
 KALLIO, A. *see* AANTAA, R. 402-409
 KALSO, E. A. *see* PALAZZO, M. G. A. 759-763
 KANTO, J. *see* AANTAA, R. 402-409
 KAO, Y. J., ZAVISCA, F. G., TELLEZ, J. M., NORTON, R. G. and RACZ, G. B. Backache after extradural anaesthesia in the postpartum period: dissection of thoracic aneurysm 335-338
 KEANE, P. W. *see* PATTERSON, K. W., (ARS) 213-214P
 KENNY, G. N. C. *see* AITKEN, H. A. 36-40; AKHTAR, T. M., (ARS) 215P; BURNS, J. W. 235-238; MARSH, B. 41-48; SKIPSEY, I. G., (ARS) 218-219P
 KERR, W. J. *see* AKHTAR, T. M., (ARS) 215P
 KESTIN, I. G. Headache after continuous spinal anaesthesia, (C) 131; Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, (C) 228; Spinal anaesthesia in obstetrics, (C) 663
 KETTLER, D. *see* KIETZMANN, D. 269-276
 KHUENL-BRADY, K. S. and WAIBEL, U. Pain on i.v. injection, (C) 506-507
 KIETZMANN, D., LARSEN, R., RATHGEBER, J., BOLTE, M. and KETTLER, D. Comparison of sufentanil-nitrous oxide anaesthesia with fentanyl-nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery 269-276
 KILPATRICK, D. C. *see* WORSLEY, M. H. 116-119
 KING, T. A. and ADAMS, A. P. Failed tracheal intubation, (C) 225
 KIRBY, F., O'DONOVAN, F., McCAUL, C., McGRATH, K., McDONALD, N. and McSHANE, A. J. Gastro-oesophageal reflux and tracheobronchial contamination in the intensive care unit, (ARS) 655P
 KIRK, A. J. B. *see* SHAW, I. H. 772-778
 KLEMENT, W. and ARNDT, J. O. Pain on injection of propofol: effects of concentration and diluent 281-284; Pain on i.v. injection, (C) 507
 KLEPPER, I. D., SANDERS, L. D. and ROSEN, M., (editors) *Ambulatory Anaesthesia and Sedation. Impairment and Recovery*, (R) 668
 KLUGER, M. T., ILSLEY, A. H., PLUMMER, J. L., BALDWIN, A. M. and OWEN, H. Pain relief and hypoxaemia during administration of extradural fentanyl by three different methods, (ARS) 656-657P
 KNEESHAW, J. D. Tension pneumothorax—wrong tube? (C) 222-223
 KNILL, R. L. Uncertainties about the ventilatory response to hypoxaemia, (C) 223-224
 KNUDSEN, L., COLD, G. E., HOLDGÅRD, H. O., JOHANSEN, U. T. and JENSEN, S. Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy 277-280
 DE KOCK, J. P. *see* REYNOLDS, K. J. 638-643
 KOEHLI, N. *see* BLACK, A. M. S., (ARS) 220P
 KOERSTER, W., KREUSCHER, M., NIESEL, H. C. and ZENZ, M., (editors) *Regional Anaesthesia*, 2nd Edn, (R) 668
 KÖLB, J. *see* LEUWER, M., (ARS) 206-207P
 KORTTILA, K. *see* LICHTOR, J. L. 579-584
 KOSCIENIAK-NIELSEN, Z. J. Intra-arterial regional analgesia, (C) 804
 KOX, W. J. *see* BROWNE, G. P. R., (ARS) 652P
 KREUSCHER, M. *see* KOERSTER, W., (R) 668
 KRINGS-ERNST, I. *see* LYNCH, J. 690-693
 KRIVOSIC-HORBER, R., ADNET, P. and REYFORD, H. Relationship between exercise-induced myolysis and malignant hyperthermia, (C) 221
 KRUPP, A. *see* LEUWER, M., (ARS) 206-207P
 KULKARNI, V. *see* CUNA, A. M. 341-345
 KUSHIMO, O. T., DAROWSKI, M. J., MORRIS, P., HOLLIS, S. and MEAKIN, G. Dose requirements of atracurium in paediatric intensive care patients 781-783
- LANDON, M. J. *see* LUMB, A. B. 106-107
 LANE, B. S. *see* LICHTOR, J. L. 579-584
 LANGTON, J., MURPHY, P., BARKER, P. and SMITH, G. A portable method to assess upper airway reactivity, (ARS) 648-649P
 LANGTON, J. *see* MURPHY, P. J., (ARS) 660-661P
 LANGTON, J. A. *see* BARKER, P., (ARS) 660P
 LARSEN, R. *see* KIETZMANN, D. 269-276
 LAURENCE, A. S. and COCKS, D. A. Serum concentrations of dantrolene following i.v. administration, (ARS) 202-203P
 LAURENCE, A. S. *see* SMITH, S. O., (ARS) 644-645P
 LAURETTI, G. R. *see* AL-MUHANDIS, W. M. 608-613
 LAZAR, E. J. *see* AMAR, D. 296-301
 LEA, K. *see* BROWNE, G. P. R., (ARS) 652P

- LEE, E. and BEN-DAVID, B. Identification of the interpleural space, (C) 130
- LEHMANN-HORN, F. and LAZZO, P. Myotonias and susceptibility to malignant hyperthermia, (C) 221-222
- LENNOX, G. *see* STEPHENS, P. H. 476-479
- LEUNG, R. K. W. *see* GIN, T. 49-53
- LEUWER, M., JANSCHON, G., KÖLB, J., KRUPP, A. and SCHNEIDER, E. Potency and ease of antagonism of pipecuronium in children, (ARS) 206-207P
- LEWIS, I. H. Inhalation induction of anaesthesia with isoflurane in children, (C) 500
- LEWIS, I. H., PRYN, S. J., REYNOLDS, P. I., PANDIT, U. A. and WILTON, N. C. T. Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction 73-78
- LICHTOR, J. L., ZACNY, J., APFELBAUM, J. L., LANE, B. S., RUPANI, G., THISTED, R. A., DOHRN, C. and KORTILA, K. Alcohol after sedation with i.v. midazolam-fentanyl: effects on psychomotor functioning 579-584
- LIST, W. F. *see* METZLER, H. 317-319
- LIU, D. W. H., STANDEN, P. and AITKENHEAD, A. R. Influence of therapeutic suggestions during general anaesthesia on recovery in patients undergoing hysterectomy, (ARS) 208-209P
- LIU, W. H. D. and AITKENHEAD, A. R. Comparison of contemporaneous and retrospective assessment of postoperative pain using the visual analogue scale 768-771
- LIDGE, J. *see* EVANS, R. D., (ARS) 217P
- LOGAN, M. R. *see* RUTHERFORD, J. S., (ARS) 647P
- LOH, L. *see* REEDER, M. K. 326-328; 626-631
- LOWRIE, A. *see* SMITH, S. O., (ARS) 644-645P
- LUMB, A. B. and LANDON, M. J. Absorption of isoflurane by silica gel 106-107
- LUMB, A. B., PETROS, A. J. and NUNN, J. F. Rib cage contribution to resting and carbon dioxide stimulated ventilation during 1 MAC isoflurane anaesthesia 712-721
- LUNN, J. Reporting of deaths, (C) 503
- LYNCH, J., KRINGS-ERNST, I., STRICK, K., TOPALIDIS, K., SCHAAF, H. and FIEBIG, M. Use of a 25-gauge Whitacre needle to reduce the incidence of postdural puncture headache 690-693
- LYONS, G. and MACDONALD, R. 29-Gauge spinal needles, (C) 222
- MCALLISTER, S. *see* WATSON, D., (ARS) 656P
- MCARDLE, C. S. *see* BURNS, J. W. 235-238
- MCCARTHY, G., STANLEY, C., COOPER, R., ELLIOTT, P. and MIRAKHUR, R. K. Dose requirements of neostigmine for antagonism of vecuronium neuromuscular block in the elderly: comparison with adults, (ARS) 652-653P
- MCCAUL, C. *see* KIRBY, F., (ARS) 655P
- MCCLOY, R., PEARSON, R., WHITWAM, J., MILLER, R., PARK, G., BELL, D. and GELLER, B. Antagonism of benzodiazepine sedation with flumazenil, (C) 504
- MCCLUNE, S., MCKAY, A. C. and CLARKE, R. S. J. Midazolam and propofol for induction of anaesthesia, (ARS) 215-216P
- MCCRORY, J. W. *see* COLEMAN, S. A. 257-261; JAMES, E. F. 323-325
- MCDONALD, N. *see* KIRBY, F., (ARS) 655P
- MACDONALD, R. *see* LYONS, G., (C) 222
- MACFIE, A. G., MAGIDES, A. D. and REILLY, C. S. Pharmacokinetics of alfentanil in burns patients, (ARS) 657P
- MACFIE, A. G., MAGIDES, A. D., RICHMOND, M. N. and REILLY, C. S. Gastric emptying in pregnancy 54-57
- MCGOWAN, S. *see* DRUMMOND, G. B., (ARS) 204P
- MCGRATH, K. *see* KIRBY, F., (ARS) 655P
- McHUGH, P. *see* ROWBOTHAM, D. J. 302-305; 421-425
- McJAMES, S. W. *see* HEINING, M. P. D. 120-126
- MCKAY, A. C. Synergism among i.v. anaesthetics, (E) 1-3
- MCKAY, A. C. *see* McCLUNE, S., (ARS) 215-216P
- MCKAY, R. *see* WENSTONE, R. 591-594
- MACKENZIE, N. *see* SKIPSEY, I. G., (ARS) 218-219P
- MCKENZIE, P. J. Deep venous thrombosis and anaesthesia, (C) 128
- McLAUCHLAN, G. A., EDMONDSON, C. and PEACOCK, J. E. Comparison of bolus or slow infusion of propofol for induction of anaesthesia in the elderly, (ARS) 211P
- McLEAN, C. F. *see* RUTTEN, A. J. 247-256; SLOAN, P. A. 378-386
- MACLEOD, A. D. *see* OATES, J. D. L., (C) 505
- McLEOD, G. A., PACE, N. and INGLIS, M. D. Bacterial growth in propofol, (C) 665-666
- McLEOD, L. J. *see* MacPHERSON, R. D. 546-552
- McLINTIC, A. J., DANSKIN, F. H., REID, J. A. and THORBURN, J. Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the foeto-placental unit during elective Caesarean section 683-689
- McLOUGHLIN, C., MIRAKHUR, R. K., TRIMBLE, E. R. and CLARKE, R. S. J. Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick 764-767
- MACPHERSON, R. D., McLEOD, L. J. and GROVE, A. J. Intra-arterial thiopentone is directly toxic to vascular endothelium 546-552
- McSHANE, A. J. *see* KIRBY, F., (ARS) 655P
- McSHARRY, C. P. *see* O'DONNELL, C. A., (ARS) 658-659P; O'DONNELL, N. G., (ARS) 661P
- MADEJ, T. H. *see* WHEATLEY, R. G. 353-359
- MADGWICK, R. *see* PALAZZO, M. G. A. 759-763
- MAEKAWA, N. *see* MIKAWA, K. 410-415; 416-420
- MAGIDES, A. D. *see* MACFIE, A. G. 54-57; (ARS) 657P
- MAGUIRE, M. *see* RYAN, T., (ARS) 204-205P
- MAHDI, A. A. L. *see* DUNDEE, J. W., (ARS) 214P
- MAHLA, E. *see* METZLER, H. 317-319
- MAHONEY, A. *see* FENNER, S. G. 483-487
- MALLARD, J. R. *see* CYNIA, A. M. 341-345
- MALMROS, C. and FLETCHER, R. Cuffed tracheal tubes for paediatric cardiac surgery cause a low incidence of postoperative airway problems, (ARS) 655P
- MANNINEN, P. H. *see* DAVIES, K. R. 58-63
- MAPLESON, W. W. *see* OKELL, R. W. 285-288
- MARAN, N. J., MARSHALL, I. and DRUMMOND, G. B. Improved method of acoustic reflection technique for upper airway measurements, (ARS) 648P
- MARKS, R. R. D., GRICE, G. A. G. and CHARTERS, P. Analysis of the shape of the laryngoscope blade, (ARS) 654P
- MARONE, G. *see* STELLATO, C. 751-758
- MARSH, A. M., NUNN, J. F., TAYLOR, S. J. and CHARLESWORTH, C. H. Airway obstruction associated with the use of the Guedel airway 517-523
- MARSH, B., WHITE, M., MORTON, N. and KENNY, G. N. C. Pharmacokinetic model driven infusion of propofol in children 41-48
- MARSHALL, I. *see* MARAN, N. J., (ARS) 648P
- MARSHALL, R. W. *see* YOSHIZUMI, J., (ARS) 212-213P; 735-740
- MARTLEW, R. *see* SMITH, S. O., (ARS) 644-645P
- MASTRONARDI, P. *see* STELLATO, C. 751-758
- MATHER, L. E. Disposition of mepivacaine and bupivacaine enantiomers in sheep 239-246
- MATHER, L. E. *see* RUTTEN, A. J. 247-256; SLOAN, P. A. 378-386
- MAURITZ, W. *see* HACKL, W., (C) 221
- MAYALL, R. *see* SNEYD, J. R., (ARS) 661-662P
- MAZUMDAR, B., TOMLINSON, A. A. and FAULDER, G. C.

- Preliminary study to assay plasma amethocaine concentrations after topical application of a new local anaesthetic cream containing amethocaine 432-436
- MAZZARELLA, B. *see* STELLATO, C. 751-758
- MEAKIN, G. Fresh gas requirement of the Bain system, (C) 663-664
- MEAKIN, G., MORTON, R. H. and WAREHAM, A. C. Age-dependent variation in response to tubocurarine in the isolated rat diaphragm, (ARS) 205-206P
- MEAKIN, G. *see* GWINNUTT, C. L. 13-16; KUSHIMO, O. T. 781-783
- MEDDINGS, J. B. *see* COOPER, P., (ARS) 201-202P
- METZLER, H., MAHLA, E., ROTMAN, B., REHAK, P., POTISK, S. and LIST, W. F. Postoperative myocardial ischaemia in patients with recent myocardial infarction 317-319
- MIKAWA, K., MAEKAWA, N., GOTO, R., KAETSU, H., HASEGAWA, M., YAKU, H. and OBARA, H. Effects of pindolol on the cardiovascular response to tracheal intubation 416-420
- MIKAWA, K., MAEKAWA, N., KAETSU, H., GOTO, R., YAKU, H. and OBARA, H. Effects of adenosine triphosphate on the cardiovascular response to tracheal intubation 410-415
- MILLER, D. Fresh gas requirement of the Bain system, (C) 664
- MILLER, D. *see* STEPHENS, P. H. 476-479
- MILLER, J. D. *see* ANDREWS, P. J. D., (ARS) 212P; 553-558
- MILLER, R. *see* McCLOY, R., (C) 504
- MILLER, R. G., (editor) *Anaesthesia*, 3rd Edn, (R) 364
- MILLIGAN, H. R. and CARP, H. Headache after continuous spinal anaesthesia, (C) 131
- MILLIGAN, K. *see* ROWBOTHAM, D. J. 302-305; 421-425
- MILLIGAN, K. R. *see* CARABINE, U. A., (ARS) 659P
- MILNE, R. W. *see* SLOAN, P. A. 378-386
- MINO, R. *see* SHARROCK, N. E. 17-25; 694-698
- MIRAKHUR, R. K. *see* MCCARTHY, G., (ARS) 652-653P; McLoughlin, C. 764-767
- MODIG, J. Deep venous thrombosis and anaesthesia, (C) 127-128; Deep venous thrombosis and anaesthesia, (C) 128
- MONK, C. *see* RAFTERY, S., (ARS) 651-652P
- MONSELL, F. *see* SMITH, S. O., (ARS) 644-645P
- MOORE, J. Assessment of the placental circulation, (E) 671-673
- MOORE, J. *see* CARABINE, U. A. 79-83; (ARS) 659P
- MORI, K. *see* NAITO, Y. 387-389
- MORRELL, D. F. *see* VAN HEERDEN, P. V. 470-472
- MORRIS, P. *see* KUSHIMO, O. T. 781-783
- MORRISON, L. M. *see* ARMSTRONG, P. J. 532-538
- MORTON, N. *see* MARSH, B. 41-48
- MORTON, R. H. *see* MEAKIN, G., (ARS) 205-206P
- MOXHAM, J. *see* AMOROSO, P., (ARS) 210P
- MOYLE, J. T. B. *see* REYNOLDS, K. J. 638-643
- MUIR, A. D., REEDER, M. K., FOËX, P., ORMEROD, O. J. M., SEAR, J. W. and JOHNSTON, C. Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population 373-377
- MUIR, A. D. *see* REEDER, M. K. 326-328; 626-631
- MURAVCHICK, S. *The Anaesthetic Plan: From Physiologic Principles to Clinical Strategies*, (R) 365
- MURIEL, C. *see* PEDRAZ, J. L. 310-316
- MURPHY, K. R. and PELTON, J. J. *ECG Essentials—A Pocket Reference for Systematic Interpretation*, (R) 364-365
- MURPHY, P. *see* BARKER, P., (ARS) 660P; LANGTON, J., (ARS) 648-649P
- MURPHY, P. G., DAVIES, M. J., MYERS, D. S. and JONES, J. G. Direct evidence for free radical generation in experimental lung injury, (ARS) 649-650P
- MURPHY, P. G., MYERS, D., WEBSTER, N. R. and JONES, J. G. The anti-oxidant potential of propofol, (ARS) 209-210P
- MURPHY, P. J., LANGTON, J., BARKER, P. and SMITH, G. Investigation of the effect of oral diazepam on upper airway reactivity, (ARS) 660-661P
- MURRAY, G. D. *see* OATES, J. D. L., (C) 505
- MURRAY, J. P. *see* PATTERSON, K. W. 108-111
- MUSHAMBI, M. C. *see* TROTTER, T. N. 748-750
- MYERS, D. *see* MURPHY, P. G., (ARS) 209-210P
- MYERS, D. S. *see* MURPHY, P. G., (ARS) 649-650P
- NAGI, H. *see* WARDE, D. J., (C) 500-501
- NAGUIB, M., ABDULATIF, M. and ABSOOD, A. Comparative effects of pipecuronium and tubocurarine on plasma concentrations of histamine in humans 320-322
- NAGUIB, M. and SARI-KOUZEL, A. Thiopentone-propofol hypnotic synergism in patients 4-6
- NAGUIB, M., SHARIF, A. M. Y., SERAJ, M., EL GAMMAL, M. and DAWLATLY, A. A. Ketamine for caudal analgesia in children: comparison with caudal bupivacaine 559-564
- NAITO, Y., TAMAI, S., SHINGU, K., FUJIMORI, R. and MORI, K. Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia 387-389
- NATION, R. L. *see* SLOAN, P. A. 378-386
- NELSON, H. *see* YOUNG, W. L. 440-446
- NEWMHAM, J. P. *see* TURNER, G. A. 306-309
- NIES, A. S. *see* GILMAN, A. G., (R) 133
- NIESEL, H. C. *see* KOERSTER, W., (R) 668
- NOBLE, D. *see* ARMSTRONG, P. J. 532-538
- NOLAN, K. M., BAXTER, M. J., WYNYARD, J. A., ROULSON, C. J. and GOLDHILL, D. R. Video surveillance of oxygen administration by mask in postoperative patients, (ARS) 650-651P
- NORTHWOOD, D., SAPSFORD, D. J., JONES, J. G., GRIFFITHS, D. and WILKINS, C. Nitrous oxide sedation causes post-hyperventilation apnoea 7-12
- NORTON, R. G. *see* KAO, Y. J. 335-338
- NUNN, J. F. Uncertainties about the ventilatory response to hypoxaemia, (C) 224
- NUNN, J. F. *see* LUMB, A. B. 712-721; MARSH, A. M. 517-523
- OATES, J. D. L., MACLEOD, A. D., OATES, P. D., PEARSALL, F. J., HOWIE, J. C. and MURRAY, G. D. Predicting difficult intubation, (C) 505
- OATES, P. D. *see* OATES, J. D. L., (C) 505
- OBARA, H. *see* MIKAWA, K. 410-415; 416-420
- O'BOYLE, C. A. *see* PATTERSON, K. W. 108-111
- O'DONNELL, C. A., O'DONNELL, N. G., MCSHARRY, C. P. and ASBURY, A. J. Comparison of the effects of anaesthetic agents on mitogen-induced lymphocyte proliferation *in vitro*, (ARS) 658-659P
- O'DONNELL, N. G., MCSHARRY, C. P., WILKINSON, P. C. and ASBURY, A. J. Comparison of the effects of propofol, midazolam and thiopentone on neutrophil polarization *in vitro*, (ARS) 661P
- O'DONNELL, N. G. *see* O'DONNELL, C. A., (ARS) 658-659P
- O'DONOVAN, F. *see* KIRBY, F., (ARS) 655P
- OKELL, R. W., MAPLESON, W. W. and VICKERS, M. D. Comparison of arterial and arterialized venous concentrations of propofol during infusion of propofol 285-288
- OOI, R., JOSHI, P. and SONI, N. Preoxygenation: use of a high flow delivery system, (ARS) 208P
- ORMEROD, O. J. M. *see* MUIR, A. D. 373-377
- O'SULLIVAN, E. P. *see* SHEARER, E. S. 569-573
- O'SULLIVAN, G. and STODDART, P. A. Failed tracheal intubation, (C) 225
- O'TOOLE, D. P. *see* PATTERSON, K. W., (ARS) 213-214P
- OWEN, H. *see* KLUGER, M. T., (ARS) 656-657P

- PACE, N. *see* McLEOD, G. A., (C) 665-666
- PALAZZO, M. G. A., KALSO, E. A., ARGIRAS, E., MADGWICK, R. and SEAR, J. W. First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model 759-763
- PANDIT, U. A. *see* LEWIS, I. H. 73-78
- PARBROOK, E. O. *see* PARBROOK, G. D., (R) 230
- PARBROOK, G. D., DAVIS, P. D. and PARBROOK, E. O., (editors) *Basic Physics and Measurement in Anaesthesia*, 3rd Edn, (R) 230
- PARK, G. *see* McCLOY, R., (C) 504
- PARK, G. R. *see* SHELLY, M. P., (C) 666
- PARKER, C. J. R. and HUNTER, J. M. Pharmacokinetics of atracurium, (C) 129
- PARNELL, C. J. *see* YOGANATHAN, S. 614-617
- PARR, S. M., ROBINSON, B. J., REES, D. and GALLETT, D. C. Interaction between betamethasone and vecuronium 447-451
- PATEL, S. *see* EVANS, R. D., (ARS) 217P
- PATIL, C. *see* STOKES, D. N. 26-35
- PATTERSON, K. W., ARMSTRONG, C., TIMON, D., O'TOOLE, D. P. and KEANE, P. W. Use of buccal prochlorperazine in the prevention of postoperative sickness, (ARS) 213-214P
- PATTERSON, K. W., CASEY, P. B., MURRAY, J. P., O'BOYLE, C. A. and CUNNINGHAM, A. J. Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam 108-111
- PEACOCK, J. E. *see* BERTHOUD, M. C. 464-466; (ARS) 645P; McLAUCHLAN, G. A., (ARS) 211P
- PEARSALL, F. J. *see* OATES, J. D. L., (C) 505
- PEARSON, J. *see* CARLI, F. 729-734
- PEARSON, J. D. *see* PETROS, A. J., (ARS) 645-646P
- PEARSON, M. *see* CARLI, F. 729-734
- PEARSON, R. *see* McCLOY, R., (C) 504
- PEDERSEN, J. Anaesthetic equipment for a developing country, (C) 360
- PEDRAZ, J. L., CALVO, M. B., GASCON, A. R., HERNANDEZ, R., MURIEL, C., TORRES, L. M. and DOMINGUEZ-GIL, A. Pharmacokinetics and distribution of ketamine after extradural administration to dogs 310-316
- PELTON, J. J. *see* MURPHY, K. R., (R) 364-365
- PETROS, A. J., BOGLE, R. G. and PEARSON, J. D. Propofol induces the production of endothelium-derived relaxing factor, (ARS) 645-646P
- PETROS, A. J. *see* LUMB, A. B. 712-721
- PHILLIPS, B. J. and HUNTER, J. M. Use of mivacurium chloride by constant infusion in the anephric patient, (ARS) 653-654P
- PIHLAJAMÄKI, K. K. Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block 621-622
- PLEUVRY, B. J. *see* AL-MUHANDIS, W. M. 608-613; STOTT, D. G. 603-607
- PLUMMER, J. L. *see* KLUGER, M. T., (ARS) 656-657P
- POLLARD, B. J. *see* SEVERN, A. M., (ARS) 650P; SNEYD, J. R., (ARS) 647P; VOHRA, A. 64-68
- POMFRET, C. J. D., SNEYD, J. R., BEECH, M. J. and HEALY, T. E. J. Variations in respiratory sinus arrhythmia may reflect levels of anaesthesia, (ARS) 646-647P
- POMFRET, C. J. D. *see* SNEYD, J. R., (ARS) 647P; (ARS) 658P
- PONTÉ J. C. *see* AMOROSO, P., (ARS) 210P; WILSON, S. R., (ARS) 216-217P
- POTISK, S. *see* METZLER, H. 317-319
- PROHOVNIK, I. *see* YOUNG, W. L. 440-446
- PRYN, S. J. *see* LEWIS, I. H. 73-78
- PRYS-ROBERTS, C. *see* DUNNET, J. M., (ARS) 214-215P; ENEVER, G., (ARS) 217-218P; RAFTERY, S., (ARS) 218P; (ARS) 651-652P
- RACZ, G. B. *see* KAO, Y. J. 335-338
- RAFTERY, S., BROWNE, B., ENEVER, G., RICHARDS, M. J. and PRYS-ROBERTS, C. Total i.v. anaesthesia with propofol and alfentanil: influence of age and weight on dose requirements, (ARS) 218P
- RAFTERY, S., WRIGHT, I., MONK, C., BOLSON, S. and PRYS-ROBERTS, C. Enoximone during coronary bypass surgery, (ARS) 651-652P
- RAFTERY, S. *see* ENEVER, G., (ARS) 217-218P; WARDE, D. J., (C) 500-501
- RALL, T. W. *see* GILMAN, A. G., (R) 133
- RALSTON, S. J. *see* HEAD-RAPSON, A. G., (ARS) 203P
- RÄSÄNEN, J. *see* ALAHUHTA, S. 678-682
- RATCLIFFE, F. M. and DORRINGTON, K. L. Pressure-volume hysteresis of the lungs in respiratory distress syndrome, (ARS) 203-204P
- RATHGERBER, J. *see* KIETZMANN, D. 269-276
- RAWLE, P. R. *see* TELFORD, R. J., (C) 503
- RAY, D. C. and DRUMMOND, G. B. Halothane hepatitis 84-99
- READ, J. R. M., DRUMMOND, G. B. and BROWN, D. T. Arterial pressure responses induced by stimuli to the upper airway in anaesthetized patients, (ARS) 216P
- REEDER, M. K., GOLDMAN, M. D., LOH, L., MUIR, A. D. and CASEY, K. R. Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen 326-328
- REEDER, M. K., MUIR, A. D., FOËX, P., GOLDMAN, M. D., LOH, L. and SMART, D. Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia 626-631
- REEDER, M. K. *see* MUIR, A. D. 373-377
- REES, D. *see* PARR, S. M. 447-451
- REHAK, P. *see* METZLER, H. 317-319
- REID, J. A. and THORBURN, J. Headache after spinal anaesthesia, (E) 674-677
- REID, J. A. *see* McLINTIC, A. J. 683-689
- REILLY, C. S. *see* BERTHOUD, M. C. 464-466; (ARS) 645P; BROOME, I. J., (ARS) 207P; GILL, N., (ARS) 649P; MACFIE, A. G. 54-57; (ARS) 657P
- RESTALL, J. *see* YOGANATHAN, S. 614-617
- REUSCHEL-JANETSCHKE, E. *see* ERDMANN, E. 178-184
- REYFORD, H. *see* KRIVOSTIC-HORBER, R., (C) 221
- REYNOLDS, F., (editor) *Epidural and Spinal Blockade in Obstetrics*, (R) 229
- REYNOLDS, K. J., DE KOCK, J. P., TARASSENKO, L. and MOYLE, J. T. B. Temperature dependence of LED and its theoretical effect on pulse oximetry 638-643
- REYNOLDS, P. I. *see* LEWIS, I. H. 73-78
- RICHARDS, M. J. *see* RAFTERY, S., (ARS) 218P
- RICHMOND, M. N. *see* MACFIE, A. G. 54-57
- RIDLEY, S. *see* AKHTAR, T. M. 632-634
- RIGG, D. L. *see* GOODIE, D. B. 329-331
- ROBERTS, G. J. and ROSENBAUM, N. L. *A Colour Atlas of Dental Analgesia and Sedation*, (R) 364
- ROBINSON, B. J. *see* PARR, S. M. 447-451
- RODGERS, E. M. Diprivan intensive care sedation in children, (C) 505
- ROE, P. G. *see* ENTWISTLE, M. D. 704-711
- ROS, P. *see* BOER, F. 69-72
- ROSE, E. L. *see* DE BONO, D. P., (E) 367-368
- ROSEN, M. *see* KLEPPER, I. D., (R) 668; SANDERS, L., (C) 504; YEE, M. K. 426-431
- ROSENBAUM, N. L. *see* ROBERTS, G. J., (R) 364
- ROTMAN, B. *see* METZLER, H. 317-319
- ROULSON, C. J. *see* NOLAN, K. M., (ARS) 650-651P
- ROWBOTHAM, D. J., MILLIGAN, K. and McHUGH, P. Effect of cisapride on morphine absorption after oral administration of sustained-release morphine 421-425; Effect of single doses of cisapride and ranitidine

- administered simultaneously on plasma concentrations of cisapride and ranitidine 302-305
- ROWBOTHAM, D. J. *see* BARKER, P., (ARS) 660P; SANDHAR, B. K., (ARS) 213P; TROTTER, T. N. 748-750
- RUNCIMAN, W. B. *see* SLOAN, P. A. 378-386
- RUPANI, G. *see* LIGHTOR, J. L. 579-584
- RUTHERFORD, J. S., LOGAN, M. R. and DRUMMOND, G. B. Change in end-expiratory respiratory volume with thiopentone or propofol induction of anaesthesia, (ARS) 647P
- RUTTEN, A. J., MATHER, L. E. and MCLEAN, C. F. Cardiovascular effects and regional clearances of i.v. bupivacaine in sheep: enantiomeric analysis 247-256
- RUTTEN, A. J. *see* SLOAN, P. A. 378-386
- RYAN, T., MAGUIRE, M., BOUCHIER-HAYES, D. and CUNNINGHAM, A. J. Left ventricular function during transoesophageal echocardiographic assessment of abdominal aortic aneurysm resection, (ARS) 204-205P
- RYDER, W. A. *see* YOUNG, J. D., (ARS) 209P
- SADDLER, J. M. Jaw stiffness—an ill understood condition, (E) 515-516
- SADLER, P. J. *see* EVANS, R. D., (ARS) 217P
- SAINT-MAURICE, C. and SHULTE STEINBERG, O., (editors) *Regional Anaesthesia in Children*, 1st Edn, (R) 132
- SALAMA, M. D. *see* AMAR, D. 296-301
- SAMUELS, T. *see* DEVLIN, J. C., (ARS) 651P
- SANDERS, D. J. *see* JEWKES, C. 788-794
- SANDERS, L., ROSEN, M. and ISAAC, P. Antagonism of benzodiazepine sedation with flumazenil, (C) 504
- SANDERS, L. D. *see* KLEPPER, I. D., (R) 668
- SANDHAR, B. K., ELLIOTT, R. H., WINDRAM, I. and ROWBOTHAM, D. J. Peripartum changes in gastric emptying, (ARS) 213P
- SAPSFORD, D. J. *see* ENTWISTLE, M. D. 704-711; JESSOP, J. 524-531; NORTHWOOD, D. 7-12
- SARANTOPOULOS, C. *see* FASSOULAKI, A. 437-439
- SARI-KOUZEL, A. *see* NAGUIB, M. 4-6
- SCHAAF, H. *see* LYNCH, J. 690-693
- SCHWEININ, M. *see* AANTAA, R. 402-409
- SCHNEIDER, E. *see* LEUWER, M., (ARS) 206-207P
- SCOTT, P. V. Identification of the interpleural space, (C) 130
- SEAR, J. W. Drug biotransformation by the kidney: how important is it, and how much do we really know? (E) 369-372
- SEAR, J. W. *see* EVANS, R. D., (ARS) 217P; JEWKES, C. 788-794; MUIR, A. D. 373-377; PALAZZO, M. G. A. 759-763
- SEBEL, P. *see* SMITH, C. 262-268
- SERAJ, M. *see* NAGUIB, M. 559-564
- SEVERN, A. M., COOLEY, J. M., JACKSON, P. W. and POLLARD, B. J. Spectral analysis of the electromyogram: effect of fentanyl, (ARS) 650P
- SHAMMOON, H. *see* AMAR, D. 296-301
- SHARIF, A. M. Y. *see* NAGUIB, M. 559-564
- SHARROCK, N. E., GO, G. and MINEO, R. Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients 694-698
- SHARROCK, N. E., MINEO, R. and URQUHART, B. Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty 17-25
- SHARWOOD-SMITH, G. H. *see* BUCHAN, A. S., (R) 509
- SHAW, I. H., KIRK, A. J. B. and CONACHER, I. D. Anaesthesia for patients with transplanted hearts and lungs undergoing non-cardiac surgery 772-778
- SHEARER, E. S., O'SULLIVAN, E. P. and HUNTER, J. M. Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration 569-573
- SHELLY, M. P. and PARK, G. R. Speed of onset of analgesia of diamorphine or morphine, (C) 666
- SHERRY, K. M. *see* WRIGHT, E. M. 585-590
- SHINGU, K. *see* NAITO, Y. 387-389
- SHORT, T. G. and CHUI, P. T. Propofol and midazolam act synergistically in combination 539-545
- SHULTE STEINBERG, O. *see* SAINT-MAURICE, C., (R) 132
- SIDHU, V. S. Interference with pacemaker function, (C) 664
- SIMON, P. J. *see* SNEYD, J. R., (ARS) 659-660P
- SINCLAIR, C. J. *see* WORSLEY, M. H. 116-119
- SINCLAIR, W. A. *see* ARMSTRONG, P. J. 532-538
- SKIPSEY, I. G., COLVIN, J. R., MACKENZIE, N. and KENNY, G. N. C. Sedation with propofol during surgery under regional block: evaluation of a computer controlled infusion system, (ARS) 218-219P
- SLOAN, P. A., MATHER, L. E., MCLEAN, C. F., RUTTEN, A. J., NATION, R. L., MILNE, R. W., RUNCIMAN, W. B. and SOMOGYI, A. A. Physiological disposition of i.v. morphine in sheep 378-386
- SMART, D. *see* REEDER, M. K. 626-631
- SMITH, C., CARTER, M., SEBEL, P. and YATE, P. Mental function after general anaesthesia for transurethral procedures 262-268
- SMITH, G. Pain after surgery, (E) 233-234
- SMITH, G. *see* LANGTON, J., (ARS) 648-649P; MURPHY, P. J., (ARS) 660-661P
- SMITH, S. O., LOWRIE, A., MARTEW, R., MONSELL, F. and LAURENCE, A. S. Morbidity following day-case procedures, (ARS) 644-645P
- SNEYD, J. R., BERRY, A., SIMON, P. J. and WRIGHT, B. Measurement of propofol metabolites in human urine using nuclear magnetic resonance, (ARS) 659-660P
- SNEYD, J. R. and MAYALL, R. Can glycopyrrolate attenuate propofol-induced hypotension in elderly patients? (ARS) 661-662P
- SNEYD, J. R., POMFRETT, C. J. D. and HEALY, T. E. J. A new perspective on intraoperative monitoring of EEG, (ARS) 658P
- SNEYD, J. R., WONG, D. Y., EDWARDS, D., POMFRETT, C. J. D., DORAN, B. R. H., HEALY, T. E. J. and POLLARD, B. J. Does physiotherapy affect the auditory evoked potentials of sedated patients in the intensive care unit? (ARS) 647P
- SNEYD, J. R. *see* POMFRETT, C. J. D., (ARS) 646-647P
- SNOWDON, S. L. *see* HEAD-RAPSON, A. G., (ARS) 203P
- SOMOGYI, A. A. *see* SLOAN, P. A. 378-386
- SONI, N. *see* OOI, R., (ARS) 208P
- SONI, N. C. *see* CHUNG, R., (ARS) 647-648P
- SPITTAL, M. J., HUNTER, S. J. and JONES, L. The pneuPAC hyperbaric variant HB: a ventilator suitable for use within a one-man hyperbaric chamber 488-491
- STANDEN, P. *see* LIU, D. W. H., (ARS) 208-209P
- STANLEY, C. *see* MCCARTHY, G., (ARS) 652-653P
- STELLATO, C., CASOLARO, V., CICCARELLI, A., MASTRONARDI, P., MAZZARELLA, B. and MARONE, G. General anaesthetics induce only histamine release selectively from human mast cells 751-758
- STEPHENS, P. H., LENNOX, G., HIRSCH, N. and MILLER, D. Superior sagittal sinus thrombosis after internal jugular vein cannulation 476-479
- STERNE, J. K. and GRANDE, C., (editors) *Trauma Anaesthesia*, (R) 508
- STEVENS, J. D. *see* WHEATLEY, R. G., (ARS) 208P
- STODDART, P. A. *see* O'SULLIVAN, G., (C) 225
- STOELTING, R. K., BARASH, P. G. and GALLAGHER, T. J., (editors) *Advances in Anaesthesia*, Vol. 7, (R) 229
- STOKES, D. N., CLUTTON-BROCK, T., PATIL, C., THOMPSON, J. M. and HUTTON, P. Comparison of invasive and

- non-invasive measurement of continuous arterial pressure using the Finapres 26-35
- STOTT, D. G. and PLEUVRY, B. J. Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice 603-607
- STRICK, K. *see* LYNCH, J. 690-693
- SWALES, J. D. Management of hyponatraemia 146-153
- SWANN, D. G. and DRUMMOND, G. B. Effect of supine and lateral positions on airway patency in anaesthetized patients, (ARS) 644P
- SWANSON BECK, J. *see* BROWN, R. A., (R) 132-133
- SWENY, P. Is postoperative oliguria avoidable? 137-145
- SYVERUD, S. A. *see* BARSAN, W. G., (R) 508-509
- TAHTA, K. *see* TEKKOK, I. H. 112-115
- TAMAI, S. *see* NAITO, Y. 387-389
- TAN, P. *see* GIN, T. 49-53
- TAN, P. S. K. *see* HACKMAN, C. H. 346-352
- TARASSENKO, L. *see* REYNOLDS, K. J. 638-643
- TATMAN, A. J., WRIGLEY, S. R. and JONES, R. M. Resistance to atracurium in a patient with an increase in plasma alpha₂ globulins 623-625
- TAYLOR, P. *see* GILMAN, A. G., (R) 133
- TAYLOR, S. J. *see* MARSH, A. M. 517-523
- TEKKOK, I. H., CATALTEPE, O., TAHTA, K. and BERTAN, V. Extradural haematoma after continuous extradural anaesthesia 112-115
- TELFORD, R. J. and RAWLE, P. R. Training in fiberoptic laryngoscopy, (C) 503
- TELLEZ, J. M. *see* KAO, Y. J. 335-338
- THISTED, R. A. *see* LIGHTOR, J. L. 579-584
- THOMAS, A. N. *see* VOHRA, A. 64-68
- THOMAS, C. *see* HASTINGS, K. L. 722-728
- THOMPSON, J. M. *see* STOKES, D. N. 26-35
- THORBURN, J. *see* McLINTIC, A. J. 683-689; REID, J. A., (E) 674-677
- TIGHE, S. Q. M. Anaesthetic equipment for a developing country, (C) 360
- TIMON, D. *see* PATTERSON, K. W., (ARS) 213-214P
- TINKER, J. and JONES, S. N., (editors) *A Pocket Book of Intensive Care: Data, Drugs and Procedures*, 2nd Edn, (R) 669
- TIPLADY, B. *see* ARMSTRONG, P. J. 532-538
- TOBIAS, M. D., HANSON III, C. W., HEPPENSTALL, R. B. and AUKBURG, S. J. Compartment syndrome after pressurized infusion 332-334
- TODD, J. G. *see* AITKEN, H. A. 36-40
- TOMLINSON, A. A. *see* MAZUMDAR, B. 432-436
- TOPALIDIS, K. *see* LYNCH, J. 690-693
- TORRES, L. M. *see* PEDRAZ, J. L. 310-316
- TRIMBLE, E. R. *see* McLoughlin, C. 764-767
- TROTTER, T. N., ROWBOTHAM, D. J., WINDRAM, I. and MUSHAMBI, M. C. Effect of sublingual buprenorphine on gastric emptying of a liquid meal 748-750
- TUNSTALL, M. E. Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, (C) 227-228
- TUNSTALL, M. E. *see* CYNIA, A. M. 341-345
- TURNER, G. A., NEWNHAM, J. P., JOHNSON, C. and WESTMORE, M. Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms 306-309
- URE, R. W., DWYER, S. J., BLOGG, C. E. and WHITE, A. P. Patient-controlled anxiety with propofol, (ARS) 657-658P
- URQUHART, B. *see* SHARROCK, N. E. 17-25
- UYS, P. C. *see* ASHTON, W. B. 741-747
- VALLIS, C. J. *see* COLEMAN, S. A. 257-261
- VAN OMMEN, H. *see* BOER, F. 69-72
- VAUGHAN, R. S. Potassium in the perioperative period 194-200
- VERHOEFF, F. *see* JEWKES, C. 788-794
- VICKERS, M. D. *see* OKELL, R. W. 285-288; YOSHIZUMI, J., (ARS) 212-213P; 735-740
- VINCENT, J.-L. Fluids for resuscitation 185-193
- VOHRA, A., THOMAS, A. N., HARPER, N. J. N. and POLLARD, B. J. Non-invasive measurement of cardiac output during induction of anaesthesia and tracheal intubation: thiopentone and propofol compared 64-68
- VUORINEN, J. *see* AANTAA, R. 402-409
- VYVYAN, H. A. L. *see* BRAUDE, N. 574-578
- WAIBEL, U. *see* KHUENL-BRADY, K. S., (C) 506-507
- WALKER, R. W. M. *see* GWINNUTT, C. L. 13-16
- WARDE, D. J., NAGI, H. and RAFTERY, S. Inhalation induction of anaesthesia with isoflurane in children, (C) 500-501
- WAREHAM, A. C. *see* MEAKIN, G., (ARS) 205-206P
- WATSON, A. *see* WATSON, D., (ARS) 656P
- WATSON, D., FARQUHAR, I. K., DENNISON, A. R., COLE, J., WATSON, A. and McALLISTER, S. Postoperative analgesia by infusion of local anaesthetic into the rectus sheath, (ARS) 656P
- WATTERS, C. *see* CAMPBELL, W., (C) 803
- WEBSTER, J., BARNARD, M. and CARLI, F. Metabolic response to colonic surgery: extradural vs continuous spinal 467-469
- WEBSTER, J. *see* CARLI, F. 729-734
- WEBSTER, N. R. *see* MURPHY, P. G., (ARS) 209-210P
- WEIBAL, E. R. *see* CRYSTAL, R. G., (R) 230
- WENSTONE, R., CAMPBELL, J. M., BOOKER, P. D. and MCKAY, R. Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine 591-594
- WEST, J. B. *see* CRYSTAL, R. G., (R) 230
- WESTENSKOW, D. R. *see* HEINING, M. P. D. 120-126
- WESTMORE, M. *see* TURNER, G. A. 306-309
- WETCHLER, B. V., (editor) *Anaesthesia for Ambulatory Surgery*, 2nd Edn, (R) 229-230
- WHEATLEY, R. G., MADEJ, T. H., JACKSON, I. J. B. and HUNTER, D. The first year's experience of an acute pain service 353-359
- WHEATLEY, R. G., STEVENS, J. D., GRACE, A. and HUNTER, D. Computerized analysis of continuous pulse oximetry in children with nocturnal breathing disorders, (ARS) 208P
- WHITE, A. P. *see* URE, R. W., (ARS) 657-658P
- WHITE, M. *see* MARSH, B. 41-48
- WHITEHEAD, J. P. *see* GOLDHILL, D. R. 289-295
- WHITWAM, J. *see* McCLOY, R., (C) 504
- WHITWAM, J. G. *see* HACKMAN, C. H. 346-352
- WILDER-SMITH, O. and BORGEAT, A. Analgesia with subhypnotic doses of thiopentone and propofol, (C) 226-227
- WILDSMITH, J. A. W. Regional anaesthesia requires attention to detail, (C) 224-225
- WILDSMITH, J. A. W. *see* ARMSTRONG, P. J. 532-538
- WILKINS, C. *see* NORTHWOOD, D. 7-12
- WILKINSON, P. C. *see* O'DONNELL, N. G., (ARS) 661P
- WILLATTS, S. M. Fluid and electrolytes revisited, (E) 135-136
- WILLIAMS, K. N. *see* CORMACK, R. R., (C) 501-502
- WILSON, S. R., AMOROSO, P., PONTÉ, J. C. and BALL, C. Resting energy expenditure in children with liver disease, (ARS) 216-217P
- WILSON, S. R. *see* AMOROSO, P., (ARS) 210P
- WILTON, N. C. T. *see* LEWIS, I. H. 73-78
- WINDRAM, I. *see* SANDHAR, B. K., (ARS) 213P; TROTTER, T. N. 748-750
- WINKLER, M. *see* HACKL, W., (C) 221

- WINYARD, J. A. *see* NOLAN, K. M., (ARS) 650-651P
 WONG, D. Y. *see* SNEYD, J. R., (ARS) 647P
 WOOD, M. Midazolam and erythromycin, (C) 131
 WOOD, P. *see* BROWNE, G. P. R., (ARS) 652P
 WORSLEY, M. H., SINCLAIR, C. J., CAMPANELLA, C.,
 KILPATRICK, D. C. and YAP, P. L. Non-cardiogenic
 pulmonary oedema after transfusion with granulocyte
 antibody containing blood: treatment with
 extracorporeal membrane oxygenation 116-119
 WRIGHT, B. *see* GILL, N., (ARS) 649P; SNEYD, J. R.,
 (ARS) 659-660P
 WRIGHT, E. M. and SHERRY, K. M. Clinical and
 haemodynamic effects of milrinone in the treatment of
 low cardiac output after cardiac surgery 585-590
 WRIGHT, I. *see* RAPTERY, S., (ARS) 651-652P
 WRIGHT, P. M. C. *see* CARABINE, U. A. 79-83
 WRIGLEY, S. R. *see* TATMAN, A. J. 623-625
- YAKU, H. *see* MIKAWA, K. 410-415; 416-420
 YAP, P. L. *see* WORSLEY, M. H. 116-119
 YATE, P. *see* SMITH, C. 262-268
 YAU, G. *see* GIN, T. 49-53
 YEE, M. K., EVANS, W. D., FACEY, P. E., HAYWARD,
 M. W. J. and ROSEN, M. Gastric emptying and small
 bowel transit in male volunteers after i.m. ketorolac
 and morphine 426-431
 YELLOWLEES, I. H. Fibreoptic sensors in clinical
 measurement 100-105
- YENTIS, S. M. and BISSONNETTE, B. P6 acupuncture and
 postoperative vomiting after tonsillectomy in children
 779-780
 YOGANATHAN, S., JOHNSTON, I. G., PARNELL, C. J.,
 HOUGHTON, I. T. and RESTALL, J. Determination of
 contamination of a chemical warfare-proof operating
 theatre with volatile anaesthetic agents and assessment
 of anaesthetic gas scavenging systems 614-617
 YOSHIZUMI, J., MARSHALL, R. W. and VICKERS, M. D.
 Effect of 5% and 10% MAC of cyclopropane and
 halothane on peak velocity of saccadic eye movements,
 (ARS) 212-213P; Effects of low concentrations of
 cyclopropane and halothane on peak velocity of
 saccadic eye movements 735-740
 YOUNG, J. D., DORRINGTON, K. L., BLAKE, G. J. P. and
 RYDER, W. A. Femoral arteriovenous extracorporeal
 removal of carbon dioxide using a hollow fibre
 membrane lung, (ARS) 209P
 YOUNG, W. L., BARKAI, A. I., PROHOVNIK, I., NELSON, H.
 and DURKIN, M. Effect of P_{aCO_2} on cerebral blood flow
 distribution during halothane compared with isoflurane
 anaesthesia in the rat 440-446
- ZACNY, J. *see* LICHTOR, J. L. 579-584
 ZAVISCA, F. G. *see* KAO, Y. J. 335-338
 ZBINDEN, A. M., FEIGENWINTER, P. and HUTMACHER, M.
 Fresh gas utilization of eight circle systems 492-499
 ZENZ, M. *see* KOERSTER, W., (R) 668
 ZICKMANN, B. *see* BOLDT, J. 595-602

SUBJECT INDEX

- A Colour Atlas of Dental Analgesia and Sedation*, ROBERTS, G. J., *et al.*, (R) 364
- A Pocket Book of Intensive Care: Data, Drugs and Procedures*, 2nd Edn, TINKER, J., *et al.*, (editors), (R) 669
- Acid-base equilibrium**, Fluid and electrolytes revisited, WILLATTS, S. M., (E) 135-136
- , Management of hyponatraemia, SWALES, J. D. 146-153
- Acid-base equilibrium, bicarbonate**, Indications for use of bicarbonate in patients with metabolic acidosis, ARIEFF, A. I. 165-177
- Acid-base equilibrium, buffers**, Indications for use of bicarbonate in patients with metabolic acidosis, ARIEFF, A. I. 165-177
- Acid-base equilibrium, metabolic acidosis**, First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model, PALAZZO, M. G. A., *et al.* 759-763
- , Indications for use of bicarbonate in patients with metabolic acidosis, ARIEFF, A. I. 165-177
- , Roles of the liver and kidney in acid-base regulation and its disorders, COHEN, R. D. 154-164
- Acid-base equilibrium, pH**, Roles of the liver and kidney in acid-base regulation and its disorders, COHEN, R. D. 154-164
- Acid-base equilibrium, respiratory acidosis**, Roles of the liver and kidney in acid-base regulation and its disorders, COHEN, R. D. 154-164
- Acupuncture**, Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction, LEWIS, I. H., *et al.* 73-78
- , P6 acupuncture and postoperative vomiting after tonsillectomy in children, YENTIS, S. M., *et al.* 779-780
- Adductor pollicis**, Antagonism of intense atracurium-induced neuromuscular block in children, GWINNUTT, C. L., *et al.* 13-16
- , Intraoperative assessment of atracurium-induced neuromuscular block using double burst stimulation, BRAUDE, N., *et al.* 574-578
- Advances in Anaesthesia*, Vol. 7, STOELTING, R. K., *et al.*, (editors), (R) 229
- Age factors**, Age-dependent variation in response to tubocurarine in the isolated rat diaphragm, MEAKIN, G., *et al.*, (ARS) 205-206P
- , Can glycopyrrolate attenuate propofol-induced hypotension in elderly patients? SNEYD, J. R., *et al.*, (ARS) 661-662P
- , Change in end-expiratory respiratory volume with thiopentone or propofol induction of anaesthesia, RUTHERFORD, J. S., *et al.*, (ARS) 647P
- , Comparison of bolus or slow infusion of propofol for induction of anaesthesia in the elderly, McLAUCHLAN, G. A., *et al.*, (ARS) 211P
- , Comparison of infusion rates of thiopentone for induction of anaesthesia in elderly patients, BERTHOUD, M. C., *et al.*, (ARS) 645P
- , Comparison of sufentanil-nitrous oxide anaesthesia with fentanyl-nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery, KRETZMANN, D., *et al.* 269-276
- , Dose requirements of neostigmine for antagonism of vecuronium neuromuscular block in the elderly: comparison with adults, MCCARTHY, G., *et al.*, (ARS) 652-653P
- , Dose requirements to suppress consciousness by continuous infusion of propofol in young adults, DUNNET, J. M., *et al.*, (ARS) 214-215P
- , Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients, SHARROCK, N. E., *et al.* 694-698
- , Mental function after general anaesthesia for transurethral procedures, SMITH, C., *et al.* 262-268
- , Total i.v. anaesthesia with propofol and alfentanil: influence of age and weight on dose requirements, RAFTERY, S., *et al.*, (ARS) 218P
- Airway, obstruction**, Airway obstruction associated with the use of the Guedel airway, MARSH, A. M., *et al.* 517-523
- , Unusual presentation of acute upper airway obstruction caused by an anterior mediastinal mass, AKHTAR, T. M., *et al.* 632-634
- Airway, patency**, Effect of supine and lateral positions on airway patency in anaesthetized patients, SWANN, D. G., *et al.*, (ARS) 644P
- , Improved method of acoustic reflection technique for upper airway measurements, MARAN, N. J., *et al.*, (ARS) 648P
- , Rib cage contribution to resting and carbon dioxide stimulated ventilation during 1 MAC isoflurane anaesthesia, LUMB, A. B., *et al.* 712-721
- Airway, pressure**, Pressure-volume hysteresis of the lungs in respiratory distress syndrome, RATCLIFFE, F. M., *et al.*, (ARS) 203-204P
- Airway, stimulation**, Arterial pressure responses induced by stimuli to the upper airway in anaesthetized patients, READ, J. R. M., *et al.*, (ARS) 216P
- Alcohol**, Alcohol after sedation with i.v. midazolam-fentanyl: effects on psychomotor functioning, LICHTOR, J. L., *et al.* 579-584
- Alkalinization**, Comparison of plain and alkalized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural Caesarean section, FERNANDO, R., *et al.* 699-703
- Allergy**, General anaesthetics induce only histamine release selectively from human mast cells, STELLATO, C., *et al.* 751-758
- Ambulatory Anaesthesia and Sedation. Impairment and Recovery*, KLEPPER, I. D., *et al.*, (editors), (R) 668
- Anaesthesia**, Potassium in the perioperative period, VAUGHAN, R. S. 194-200
- Anaesthesia*, 3rd Edn, MILLER, R. G., (editor), (R) 364
- Anaesthesia, day-case**, Alcohol after sedation with i.v. midazolam-fentanyl: effects on psychomotor functioning, LICHTOR, J. L., *et al.* 579-584
- , Morbidity following day-case procedures, SMITH, S. O., *et al.*, (ARS) 644-645P
- , Rapid inhalation induction with isoflurane in humidified carrier gas, VAN HEERDEN, P. V., *et al.* 470-472
- Anaesthesia, dental**, Rapid inhalation induction with isoflurane in humidified carrier gas, VAN HEERDEN, P. V., *et al.* 470-472
- Anaesthesia, depth**, A new perspective on intraoperative monitoring of EEG, SNEYD, J. R., *et al.*, (ARS) 658P

- , Does physiotherapy affect the auditory evoked potentials of sedated patients in the intensive care unit? SNEYD, J. R., *et al.*, (ARS) 647P
- , Systolic arterial pressure as a monitor of depth of anaesthesia, ASBURY, A. J., (C) 506
- , Systolic arterial pressure as a monitor of depth of anaesthesia, COUTO DA SILVA, J. M., (C) 506
- , Variations in respiratory sinus arrhythmia may reflect levels of anaesthesia, POMFRETT, C. J. D., *et al.*, (ARS) 646–647P
- Anaesthesia for Ambulatory Surgery**, 2nd Edn, WETCHLER, B. V., (editor), (R) 229–230
- Anaesthesia, general**, Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia, DELAUNAY, L., *et al.* 397–401
- , Effects of labetalol on perioperative stress markers and isoflurane requirements, AMAR, D., *et al.* 296–301
- , General anaesthetics induce only histamine release selectively from human mast cells, STELLATO, C., *et al.* 751–758
- , Mental function after general anaesthesia for transurethral procedures, SMITH, C., *et al.* 262–268
- , Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, BARKER, P., *et al.*, (ARS) 660P
- Anaesthesia, geriatric**, Can glycopyrrolate attenuate propofol-induced hypotension in elderly patients? SNEYD, J. R., *et al.*, (ARS) 661–662P
- , Comparison of bolus or slow infusion of propofol for induction of anaesthesia in the elderly, McLAUCHLAN, G. A., *et al.*, (ARS) 211P
- , Comparison of infusion rates of thiopentone for induction of anaesthesia in elderly patients, BERTHOUD, M. C., *et al.*, (ARS) 645P
- , Comparison of sufentanil–nitrous oxide anaesthesia with fentanyl–nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery, KRETZMANN, D., *et al.* 269–276
- , Dose requirements of neostigmine for antagonism of vecuronium neuromuscular block in the elderly: comparison with adults, MCCARTHY, G., *et al.*, (ARS) 652–653P
- , Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients, SHARROCK, N. E., *et al.* 694–698
- Anaesthesia, neurosurgical**, Controlled hypotension for cerebral aneurysm surgery in the presence of severe aortic coarctation, GOODIE, D. B., *et al.* 329–331
- , Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy, KNUDSEN, L., *et al.* 277–280
- Anaesthesia, obstetric**, Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section, ASHTON, W. B., *et al.* 741–747
- , Backache after extradural anaesthesia in the postpartum period: dissection of thoracic aneurysm, KAO, Y. J., *et al.* 335–338
- , Comparison of plain and alkalized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural Caesarean section, FERNANDO, R., *et al.* 699–703
- , Disposition of propofol at Caesarean section and in the postpartum period, GIN, T., *et al.* 49–53
- , Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the feto-placental unit during elective Caesarean section, McLINTIC, A. J., *et al.* 683–689
- , Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms, TURNER, G. A., *et al.* 306–309
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678–682
- , Failed tracheal intubation, KING, T. A., *et al.*, (C) 225
- , Failed tracheal intubation, O'SULLIVAN, G., *et al.*, (C) 225
- , First use of combined spinal–extradural anaesthesia, CARRIE, L. E. S., (C) 667
- , First use of combined spinal–extradural anaesthesia, ELDOR, J., (C) 666
- , 29-Gauge spinal needles, LYONS, G., *et al.*, (C) 222
- , Headache after continuous spinal anaesthesia, KESTIN, I. G., (C) 131
- , Headache after continuous spinal anaesthesia, MILLIGAN, H. R., *et al.*, (C) 131
- , Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, KESTIN, I. G., (C) 228
- , Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, TUNSTALL, M. E., (C) 227–228
- , Influence of therapeutic suggestions during general anaesthesia on recovery in patients undergoing hysterectomy, LIU, D. W. H., *et al.*, (ARS) 208–209P
- , Management of labour and delivery in patients with intracranial neoplasms, FINFER, S. R. 784–787
- , Maternal temperature regulation during extradural analgesia for labour, CAMANN, W. R., *et al.* 565–568
- , Peripartum changes in gastric emptying, SANDHAR, B. K., *et al.*, (ARS) 213P
- , Spinal anaesthesia in obstetrics, BROWNIDGE, P., (C) 663
- , Spinal anaesthesia in obstetrics, KESTIN, I. G., (C) 663
- , The loading dose in continuous infusion extradural analgesia in obstetrics, JAMES, E. F., *et al.* 323–325
- Anaesthesia, outpatient**, Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia, NAITO, Y., *et al.* 387–389
- Anaesthesia, paediatric**, Antagonism of intense atracurium-induced neuromuscular block in children, GWINNUTT, C. L., *et al.* 13–16
- , Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia, NAITO, Y., *et al.* 387–389
- , Cuffed tracheal tubes for paediatric cardiac surgery cause a low incidence of postoperative airway problems, MALMROS, C., *et al.*, (ARS) 655P
- , Diprivan intensive care sedation in children, RODGERS, E. M., (C) 505
- , Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction, LEWIS, I. H., *et al.* 73–78
- , Fresh gas requirement of the Bain system, MEAKIN, G., (C) 663–664
- , Fresh gas requirement of the Bain system, MILLER, D., (C) 664
- , Inhalation induction of anaesthesia with isoflurane: effect of added carbon dioxide, COLEMAN, S. A., *et al.* 257–261
- , Inhalation induction of anaesthesia with isoflurane in children, LEWIS, I. H., (C) 500
- , Inhalation induction of anaesthesia with isoflurane in children, WARDE, D. J., *et al.*, (C) 500–501
- , P6 acupuncture and postoperative vomiting after tonsillectomy in children, YENTIS, S. M., *et al.* 779–780
- , Pharmacokinetic model driven infusion of propofol in children, MARSH, B., *et al.* 41–48
- Anaesthetic techniques, conduction**, Anaesthesia and bone marrow aplasia, FENNER, S. G., *et al.*, (C) 665
- , Anaesthesia and bone marrow aplasia, HAMILTON, W. K., (C) 665

- Anaesthetic techniques, extradural**, Backache after extradural anaesthesia in the postpartum period: dissection of thoracic aneurysm, KAO, Y. J., *et al.* 335-338
- , Comparison of plain and alkalized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural Caesarean section, FERNANDO, R., *et al.* 699-703
- , Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the foeto-placental unit during elective Caesarean section, McLINTIC, A. J., *et al.* 683-689
- , Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients, SHARROCK, N. E., *et al.* 694-698
- , Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms, TURNER, G. A., *et al.* 306-309
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678-682
- , Extradural haematoma after continuous extradural anaesthesia, TEKKOK, I. H., *et al.* 112-115
- , First use of combined spinal-extradural anaesthesia, CARRIE, L. E. S., (C) 667
- , First use of combined spinal-extradural anaesthesia, ELDOR, J., (C) 666
- , Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty, SHARROCK, N. E., *et al.* 17-25
- , Maternal temperature regulation during extradural analgesia for labour, CAMANN, W. R., *et al.* 565-568
- , Metabolic response to colonic surgery: extradural *vs* continuous spinal, WEBSTER, J., *et al.* 467-469
- , Pharmacokinetics and distribution of ketamine after extradural administration to dogs, PEDRAZ, J. L., *et al.* 310-316
- , Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic, CARLI, F., *et al.* 729-734
- , The first year's experience of an acute pain service, WHEATLEY, R. G., *et al.* 353-359
- , The loading dose in continuous infusion extradural analgesia in obstetrics, JAMES, E. F., *et al.* 323-325
- Anaesthetic techniques, extradural, test doses**, Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, KESTIN, I. G., (C) 228
- , Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, TUNSTALL, M. E., (C) 227-228
- Anaesthetic techniques, fibreoptic**, Training in fibreoptic laryngoscopy, BRIMACOMBE, J., (C) 503
- , Training in fibreoptic laryngoscopy, TELFORD, R. J., *et al.* (C) 503
- Anaesthetic techniques, hypotensive**, Comparison of the Finapres and direct arterial pressure monitoring during profound hypotensive anaesthesia, AITKEN, H. A., *et al.* 36-40
- , Controlled hypotension for cerebral aneurysm surgery in the presence of severe aortic coarctation, GOODIE, D. B., *et al.* 329-331
- , Effects of adenosine triphosphate on the cardiovascular response to tracheal intubation, MIKAWA, K., *et al.* 410-415
- , Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty, SHARROCK, N. E., *et al.* 17-25
- , Repair of traumatic transection of the thoracic aorta: esmolol for intraoperative control of arterial pressure, FENNER, S. G., *et al.* 483-487
- Anaesthetic techniques, induction**, Comparison of bolus or slow infusion of propofol for induction of anaesthesia in the elderly, McLAUCHLAN, G. A., *et al.* (ARS) 211P
- , Haemodynamic effects of propofol: induction with 2.5 mg kg⁻¹, FAIRFIELD, J. E., *et al.* 618-620
- , Inhalation induction of anaesthesia with isoflurane: effect of added carbon dioxide, COLEMAN, S. A., *et al.* 257-261
- , Inhalation induction of anaesthesia with isoflurane in children, LEWIS, I. H., (C) 500
- , Inhalation induction of anaesthesia with isoflurane in children, WARDE, D. J., *et al.* (C) 500-501
- , Midazolam and propofol for induction of anaesthesia, McCLUNE, S., *et al.* (ARS) 215-216P
- , Propofol and midazolam act synergistically in combination, SHORT, T. G., *et al.* 539-545
- , Rapid inhalation induction with isoflurane in humidified carrier gas, VAN HEERDEN, P. V., *et al.* 470-472
- Anaesthetic techniques, inhalation**, Inhalation induction of anaesthesia with isoflurane: effect of added carbon dioxide, COLEMAN, S. A., *et al.* 257-261
- , Inhalation induction of anaesthesia with isoflurane in children, LEWIS, I. H., (C) 500
- , Inhalation induction of anaesthesia with isoflurane in children, WARDE, D. J., *et al.* (C) 500-501
- Anaesthetic techniques, i.v. bolus**, Comparison of bolus or slow infusion of propofol for induction of anaesthesia in the elderly, McLAUCHLAN, G. A., *et al.* (ARS) 211P
- Anaesthetic techniques, i.v. infusion**, Comparison of arterial and arterialized venous concentrations of propofol during infusion of propofol, OKELL, R. W., *et al.* 285-288
- , Comparison of bolus or slow infusion of propofol for induction of anaesthesia in the elderly, McLAUCHLAN, G. A., *et al.* (ARS) 211P
- , Comparison of infusion rates of thiopentone for induction of anaesthesia in elderly patients, BERTHOUD, M. C., *et al.* (ARS) 645P
- , Comparison of thiopentone and propofol at two rates of administration in patients with severe head injury, ANDREWS, P. J. D., *et al.* (ARS) 212P
- , Dose requirements to suppress consciousness by continuous infusion of propofol in young adults, DUNNET, J. M., *et al.* (ARS) 214-215P
- , Hyperventilation and blood concentrations of propofol during total i.v. anaesthesia, ENEVER, G., *et al.* (ARS) 217-218P
- , Pharmacokinetic model driven infusion of propofol in children, MARSH, B., *et al.* 41-48
- , Sedation with propofol during surgery under regional block: evaluation of a computer controlled infusion system, SKIPSEY, I. G., *et al.* (ARS) 218-219P
- Anaesthetic techniques, loading dose**, The loading dose in continuous infusion extradural analgesia in obstetrics, JAMES, E. F., *et al.* 323-325
- Anaesthetic techniques, local**, Intra-arterial regional analgesia, AUSTIN, T. R., (C) 803
- , Intra-arterial regional analgesia, GILSANZ, F., (C) 803-804
- , Intra-arterial regional analgesia, KOSCIELNIAK-NIELSEN, Z. J., (C) 804
- Anaesthetic techniques, preoxygenation**, Effectiveness of preoxygenation in morbidly obese patients, BERTHOUD, M. C., *et al.* 464-466
- , Preoxygenation: use of a high flow delivery system, OOI, R., *et al.* (ARS) 208P

- Anaesthetic techniques, regional**, Regional anaesthesia requires attention to detail, IRVINS, F. A., (C) 225
- , Regional anaesthesia requires attention to detail, WILDSMITH, J. A. W., (C) 224–225
- , Sedation with propofol during surgery under regional block: evaluation of a computer controlled infusion system, SKIPSEY, I. G., *et al.*, (ARS) 218–219P
- Anaesthetic techniques, regional, brachial plexus**, Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block, PHILAJAMAKI, K. K. 621–622
- , Unsuspected extradural catheterization in an interscalene block, COOK, L. B. 473–475
- Anaesthetic techniques, regional, caudal**, Ketamine for caudal analgesia in children: comparison with caudal bupivacaine, NAGUB, M., *et al.* 559–564
- Anaesthetic techniques, regional, paravertebral block**, Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704–711
- Anaesthetic techniques, regional, rectus sheath**, Postoperative analgesia by infusion of local anaesthetic into the rectus sheath, WATSON, D., *et al.*, (ARS) 656P
- Anaesthetic techniques, subarachnoid**, First use of combined spinal–extradural anaesthesia, CARRIE, L. E. S., (C) 667
- , First use of combined spinal–extradural anaesthesia, ELDOR, J., (C) 666
- , Headache after spinal anaesthesia, REID, J. A., *et al.*, (E) 674–677
- , Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, KESTIN, I. G., (C) 228
- , Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, TUNSTALL, M. E., (C) 227–228
- , Metabolic response to colonic surgery: extradural vs continuous spinal, WEBSTER, J., *et al.* 467–469
- , Spinal anaesthesia in obstetrics, BROWNRIDGE, P., (C) 663
- , Spinal anaesthesia in obstetrics, KESTIN, I. G., (C) 663
- , Systemic fentanyl enhances the spread of spinal analgesia produced by lignocaine, FASSOULAKI, A., *et al.* 437–439
- , Use of a 25-gauge Whitacre needle to reduce the incidence of postdural puncture headache, LYNCH, J., *et al.* 690–693
- Anaesthetic techniques, subarachnoid, complications**, Headache after continuous spinal anaesthesia, KESTIN, I. G., (C) 131
- , Headache after continuous spinal anaesthesia, MILLIGAN, H. R., *et al.*, (C) 131
- , Transient ischaemic attack after spinal anaesthesia, CHUNG, R. A., *et al.* 635–637
- Anaesthetic techniques, topical**, Preliminary study to assay plasma amethocaine concentrations after topical application of a new local anaesthetic cream containing amethocaine, MAZUMDAR, B., *et al.* 432–436
- Anaesthetic techniques, total**, Total i.v. anaesthesia with propofol and alfentanil: influence of age and weight on dose requirements, RAFTERY, S., *et al.*, (ARS) 218P
- Anaesthetics gases, cyclopropane**, Effect of 5% and 10% MAC of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.*, (ARS) 212–213P
- , Effects of low concentrations of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.* 735–740
- Anaesthetics gases, nitrous oxide**, Anaesthesia and bone marrow aplasia, FENNER, S. G., *et al.*, (C) 665
- , Anaesthesia and bone marrow aplasia, HAMILTON, W. K., (C) 665
- , Changes in amplitude and latency of the P300 component of the auditory evoked potential with sedative and anaesthetic concentrations of nitrous oxide, JESSOP, J., *et al.* 524–531
- , Effect of 5% and 10% MAC of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.*, (ARS) 212–213P
- , Neuromuscular and clinical effects of mivacurium chloride in healthy adult patients during nitrous oxide–enflurane anaesthesia, GOLDHILL, D. R., *et al.* 289–295
- , Nitrous oxide sedation causes post-hyperventilation apnoea, NORTHWOOD, D., *et al.* 7–12
- , Rapid inhalation induction with isoflurane in humidified carrier gas, VAN HEERDEN, P. V., *et al.* 470–472
- Anaesthetics, i.v.**, Synergism among i.v. anaesthetics, MCKAY, A. C., (E) 1–3
- Anaesthetics i.v., etomidate**, Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass, BOER, F., *et al.* 69–72
- , Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanose and strychnine, AL-MUHANDIS, W. M., *et al.* 608–613
- Anaesthetics i.v., ketamine**, General anaesthetics induce only histamine release selectively from human mast cells, STELLATO, C., *et al.* 751–758
- , Ketamine for caudal analgesia in children: comparison with caudal bupivacaine, NAGUB, M., *et al.* 559–564
- , Pharmacokinetics and distribution of ketamine after extradural administration to dogs, PEDRAZ, J. L., *et al.* 310–316
- Anaesthetics i.v., methohexitone**, Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanose and strychnine, AL-MUHANDIS, W. M., *et al.* 608–613
- Anaesthetics i.v., morphine**, Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704–711
- Anaesthetics i.v., propofol**, Analgesia with subhypnotic doses of thiopentone and propofol, ARENDT-NIELSEN, L., *et al.*, (C) 227
- , Analgesia with subhypnotic doses of thiopentone and propofol, WILDER-SMITH, O., *et al.*, (C) 226–227
- , Bacterial growth in propofol, MCLEOD, G. A., *et al.*, (C) 665–666
- , Can glycopyrrrolate attenuate propofol-induced hypotension in elderly patients? SNEYD, J. R., *et al.*, (ARS) 661–662P
- , Change in end-expiratory respiratory volume with thiopentone or propofol induction of anaesthesia, RUTHERFORD, J. S., *et al.*, (ARS) 647P
- , Comparison of arterial and arterialized venous concentrations of propofol during infusion of propofol, OKELL, R. W., *et al.* 285–288
- , Comparison of bolus or slow infusion of propofol for induction of anaesthesia in the elderly, McLAUCHLAN, G. A., *et al.*, (ARS) 211P
- , Comparison of the effects of anaesthetic agents on mitogen-induced lymphocyte proliferation *in vitro*, O'DONNELL, C. A., *et al.*, (ARS) 658–659P
- , Comparison of the effects of propofol, midazolam and thiopentone on neutrophil polarization *in vitro*, O'DONNELL, N. G., *et al.*, (ARS) 661P
- , Comparison of thiopentone and propofol at two rates of administration in patients with severe head injury, ANDREWS, P. J. D., *et al.*, (ARS) 212P
- , Desaturation and induction characteristics: comparison of propofol and thiopentone during mask

- anaesthesia with isoflurane, HEAD-RAPSON, A. G., *et al.*, (ARS) 203P
- , Diprivan intensive care sedation in children, RODGERS, E. M., (C) 505
- , Disposition of propofol at Caesarean section and in the postpartum period, GIN, T., *et al.* 49–53
- , Does physiotherapy affect the auditory evoked potentials of sedated patients in the intensive care unit? SNEYD, J. R., *et al.*, (ARS) 647P
- , Dose requirements to suppress consciousness by continuous infusion of propofol in young adults, DUNNET, J. M., *et al.*, (ARS) 214–215P
- , Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass, BOER, F., *et al.* 69–72
- , General anaesthetics induce only histamine release selectively from human mast cells, STELLATO, C., *et al.* 751–758
- , Haemodynamic effects of propofol: induction with 2.5 mg kg⁻¹, FAIRFIELD, J. E., *et al.* 618–620
- , Hyperventilation and blood concentrations of propofol during total i.v. anaesthesia, ENEVER, G., *et al.*, (ARS) 217–218P
- , Measurement of propofol metabolites in human urine using nuclear magnetic resonance, SNEYD, J. R., *et al.*, (ARS) 659–660P
- , Midazolam and propofol for induction of anaesthesia, MCCLUNE, S., *et al.*, (ARS) 215–216P
- , Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanose and strychnine, AL-MUHANDIS, W. M., *et al.* 608–613
- , Non-invasive measurement of cardiac output during induction of anaesthesia and tracheal intubation: thiopentone and propofol compared, VOHRA, A., *et al.* 64–68
- , Pain on injection of propofol: effects of concentration and diluent, KLEMENT, W., *et al.* 281–284
- , Patient-controlled analgesia with propofol, URE, R. W., *et al.*, (ARS) 657–658P
- , Pharmacokinetic model driven infusion of propofol in children, MARSH, B., *et al.* 41–48
- , Propofol and midazolam act synergistically in combination, SHORT, T. G., *et al.* 539–545
- , Propofol induces the production of endothelium-derived relaxing factor, PETROS, A. J., *et al.*, (ARS) 645–646P
- , Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam, PATTERSON, K. W., *et al.* 108–111
- , Sedation with propofol during surgery under regional block: evaluation of a computer controlled infusion system, SKIPSEY, I. G., *et al.*, (ARS) 218–219P
- , The anti-oxidant potential of propofol, MURPHY, P. G., *et al.*, (ARS) 209–210P
- , Thiopentone-propofol hypnotic synergism in patients, NAGUIB, M., *et al.* 4–6
- , Total i.v. anaesthesia with propofol and alfentanil: influence of age and weight on dose requirements, RAFTERY, S., *et al.*, (ARS) 218P
- Anaesthetics i.v., thiopentone**, Anaesthetic-plasma interactions: a study using nuclear magnetic resonance spectroscopy (MRS), EVANS, R. D., *et al.*, (ARS) 217P
- , Analgesia with subhypnotic doses of thiopentone and propofol, ARENDT-NIELSEN, L., *et al.*, (C) 227
- , Analgesia with subhypnotic doses of thiopentone and propofol, WILDER-SMITH, O., *et al.*, (C) 226–227
- , Change in end-expiratory respiratory volume with thiopentone or propofol induction of anaesthesia, RUTHERFORD, J. S., *et al.*, (ARS) 647P
- , Comparison of infusion rates of thiopentone for induction of anaesthesia in elderly patients, BERTHOUD, M. C., *et al.*, (ARS) 645P
- , Comparison of the effects of anaesthetic agents on mitogen-induced lymphocyte proliferation *in vitro*, O'DONNELL, C. A., *et al.*, (ARS) 658–659P
- , Comparison of the effects of propofol, midazolam and thiopentone on neutrophil polarization *in vitro*, O'DONNELL, N. G., *et al.*, (ARS) 661P
- , Comparison of thiopentone and propofol at two rates of administration in patients with severe head injury, ANDREWS, P. J. D., *et al.*, (ARS) 212P
- , Desaturation and induction characteristics: comparison of propofol and thiopentone during mask anaesthesia with isoflurane, HEAD-RAPSON, A. G., *et al.*, (ARS) 203P
- , Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass, BOER, F., *et al.* 69–72
- , General anaesthetics induce only histamine release selectively from human mast cells, STELLATO, C., *et al.* 751–758
- , Intra-arterial thiopentone is directly toxic to vascular endothelium, MACPHERSON, R. D., *et al.* 546–552
- , Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanose and strychnine, AL-MUHANDIS, W. M., *et al.* 608–613
- , Non-invasive measurement of cardiac output during induction of anaesthesia and tracheal intubation: thiopentone and propofol compared, VOHRA, A., *et al.* 64–68
- , Thiopentone-propofol hypnotic synergism in patients, NAGUIB, M., *et al.* 4–6
- Anaesthetics local, amethocaine**, Preliminary study to assay plasma amethocaine concentrations after topical application of a new local anaesthetic cream containing amethocaine, MAZUMDAR, B., *et al.* 432–436
- Anaesthetics local, bupivacaine**, Cardiovascular effects and regional clearances of i.v. bupivacaine in sheep: enantiomeric analysis, RUTTEN, A. J., *et al.* 247–256
- , Disposition of mepivacaine and bupivacaine enantiomers in sheep, MATHER, L. E. 239–246
- , Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients, SHARROCK, N. E., *et al.* 694–698
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678–682
- , First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model, PALAZZO, M. G. A., *et al.* 759–763
- , Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, KESTIN, I. G., (C) 228
- , Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia, TUNSTALL, M. E., (C) 227–228
- , Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block, PIHLAJAMÄKI, K. K. 621–622
- , Ketamine for caudal analgesia in children: comparison with caudal bupivacaine, NAGUIB, M., *et al.* 559–564
- , Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704–711
- , Postoperative analgesia by infusion of local anaesthetic into the rectus sheath, WATSON, D., *et al.*, (ARS) 656P
- , Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic, CARLI, F., *et al.* 729–734
- , The loading dose in continuous infusion extradural analgesia in obstetrics, JANES, E. F., *et al.* 323–325

- Anaesthetics local, lignocaine**, Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the feto-placental unit during elective Caesarean section, McLINTIC, A. J., *et al.* 683-689
- , Effects of i.v. lignocaine on psychological performance and subjective state in healthy volunteers, ARMSTRONG, P. J., *et al.* 532-538
- , Systemic fentanyl enhances the spread of spinal analgesia produced by lignocaine, FASSOULAKI, A., *et al.* 437-439
- Anaesthetics local, lignocaine-bupivacaine**, Comparison of plain and alkalinized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural Caesarean section, FERNANDO, R., *et al.* 699-703
- Anaesthetics local, mepivacaine**, Disposition of mepivacaine and bupivacaine enantiomers in sheep, MATHER, L. E. 239-246
- Anaesthetics local, stereoisomers**, Cardiovascular effects and regional clearances of i.v. bupivacaine in sheep: enantiomeric analysis, RUTTEN, A. J., *et al.* 247-256
- , Disposition of mepivacaine and bupivacaine enantiomers in sheep, MATHER, L. E. 239-246
- Anaesthetics volatile, enflurane**, Neuromuscular and clinical effects of mivacurium chloride in healthy adult patients during nitrous oxide-enflurane anaesthesia, GOLDHILL, D. R., *et al.* 289-295
- Anaesthetics volatile, halothane**, Anaesthetic-plasma interactions: a study using nuclear magnetic resonance spectroscopy (MRS), EVANS, R. D., *et al.*, (ARS) 217P
- , Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia, NAITO, Y., *et al.* 387-389
- , Effect of 5% and 10% MAC of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.*, (ARS) 212-213P
- , Effect of P_{aCO_2} on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat, YOUNG, W. L., *et al.* 440-446
- , Effects of low concentrations of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.* 735-740
- , Halothane hepatitis, RAY, D. C., *et al.* 84-99
- , Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick, McLOUGHLIN, C., *et al.* 764-767
- , Screening for antibodies associated with halothane hepatitis, HASTINGS, K. L., *et al.* 722-728
- Anaesthetics volatile, isoflurane**, Absorption of isoflurane by silica gel, LUMB, A. B., *et al.* 106-107
- , Desaturation and induction characteristics: comparison of propofol and thiopentone during mask anaesthesia with isoflurane, HEAD-RAPSON, A. G., *et al.*, (ARS) 203P
- , Effect of P_{aCO_2} on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat, YOUNG, W. L., *et al.* 440-446
- , Effects of labetalol on perioperative stress markers and isoflurane requirements, AMAR, D., *et al.* 296-301
- , Haemodynamic and oxygen transport effects of isoflurane as sedation in ventilated patients in the intensive care unit, BROWNE, G. P. R., *et al.*, (ARS) 652P
- , Inhalation induction of anaesthesia with isoflurane: effect of added carbon dioxide, COLEMAN, S. A., *et al.* 257-261
- , Inhalation induction of anaesthesia with isoflurane in children, LEWIS, I. H., (C) 500
- , Inhalation induction of anaesthesia with isoflurane in children, WARDE, D. J., *et al.*, (C) 500-501
- , Rapid inhalation induction with isoflurane in humidified carrier gas, VAN HEERDEN, P. V., *et al.* 470-472
- , Rib cage contribution to resting and carbon dioxide stimulated ventilation during 1 MAC isoflurane anaesthesia, LUMB, A. B., *et al.* 712-721
- Anaesthetics volatile, sevoflurane**, Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia, NAITO, Y., *et al.* 387-389
- Anaesthetics volatile, trace concentrations**, Determination of contamination of a chemical warfare-proof operating theatre with volatile anaesthetic agents and assessment of anaesthetic gas scavenging systems, YOGANATHAN, S., *et al.* 614-617
- Analgesia, obstetric**, The loading dose in continuous infusion extradural analgesia in obstetrics, JAMES, E. F., *et al.* 323-325
- Analgesia, paediatric**, Ketamine for caudal analgesia in children: comparison with caudal bupivacaine, NAGUIB, M., *et al.* 559-564
- Analgesia, patient-controlled**, Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac, BURNS, J. W., *et al.* 235-238
- , Pain relief and hypoxaemia during administration of extradural fentanyl by three different methods, KLUGER, M. T., *et al.*, (ARS) 656-657P
- , Patient-controlled analgesia with propofol, URE, R. W., *et al.*, (ARS) 657-658P
- , The first year's experience of an acute pain service, WHEATLEY, R. G., *et al.* 353-359
- Analgesia, postoperative**, Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac, BURNS, J. W., *et al.* 235-238
- , Ketamine for caudal analgesia in children: comparison with caudal bupivacaine, NAGUIB, M., *et al.* 559-564
- , Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704-711
- , Postoperative analgesia by infusion of local anaesthetic into the rectus sheath, WATSON, D., *et al.*, (ARS) 656P
- Analgesic techniques, extradural**, The loading dose in continuous infusion extradural analgesia in obstetrics, JAMES, E. F., *et al.* 323-325
- Analgesic techniques, infusion**, Pain relief and hypoxaemia during administration of extradural fentanyl by three different methods, KLUGER, M. T., *et al.*, (ARS) 656-657P
- Analgesic techniques, regional, i.a.**, Intra-arterial regional analgesia, AUSTIN, T. R., (C) 803
- , Intra-arterial regional analgesia, GILSANZ, F., (C) 803-804
- , Intra-arterial regional analgesia, KOSCIELNIAK-NIELSEN, Z. J., (C) 804
- Analgesic techniques, subhypnotic dose**, Analgesia with subhypnotic doses of thiopentone and propofol, ARENDT-NIELSEN, L., *et al.*, (C) 227
- , Analgesia with subhypnotic doses of thiopentone and propofol, WILDER-SMITH, O., *et al.*, (C) 226-227
- Analgesics non-opioid, diclofenac**, Venous sequelae after i.v. diclofenac, CAMPBELL, W., *et al.*, (C) 803
- , Venous sequelae after i.v. diclofenac, GOPINATH, R., (C) 803
- Analgesics non-opioid, ketorolac**, Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac, BURNS, J. W., *et al.* 235-238
- , Gastric emptying and small bowel transit in male volunteers after i.m. ketorolac and morphine, YEE, M. K., *et al.* 426-431
- Analgesics opioid, alfentanil**, Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric

- patients undergoing Caesarean section, ASHTON, W. B., *et al.* 741-747
- , Pharmacokinetics of alfentanil in burns patients, MACFIE, A. G., *et al.*, (ARS) 657P
- , Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice, STOTT, D. G., *et al.* 603-607
- , Total i.v. anaesthesia with propofol and alfentanil: influence of age and weight on dose requirements, RAFTERY, S., *et al.*, (ARS) 218P
- Analgesics opioid, buprenorphine**, Effect of sublingual buprenorphine on gastric emptying of a liquid meal, TROTTER, T. N., *et al.* 748-750
- Analgesics opioid, diamorphine**, Speed of onset of analgesia of diamorphine or morphine, SHELLY, M. P., *et al.*, (C) 666
- Analgesics opioid, etorphine**, Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice, STOTT, D. G., *et al.* 603-607
- Analgesics opioid, fentanyl**, Alcohol after sedation with i.v. midazolam-fentanyl: effects on psychomotor functioning, LICHTOR, J. L., *et al.* 579-584
- , Comparison of sufentanil-nitrous oxide anaesthesia with fentanyl-nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery, KIETZMANN, D., *et al.* 269-276
- , Does physiotherapy affect the auditory evoked potentials of sedated patients in the intensive care unit? SNEYD, J. R., *et al.*, (ARS) 647P
- , Maternal temperature regulation during extradural analgesia for labour, CAMANN, W. R., *et al.* 565-568
- , Pain relief and hypoxaemia during administration of extradural fentanyl by three different methods, KLUGER, M. T., *et al.*, (ARS) 656-657P
- , Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice, STOTT, D. G., *et al.* 603-607
- , Spectral analysis of the electromyogram: effect of fentanyl, SEVERN, A. M., *et al.*, (ARS) 650P
- , Spinally mediated antinociceptive effects of xylazine, an alpha-2 adrenoceptor agonist: interaction with spinal cord opioid pathways, GOODCHILD, C. S., *et al.*, (ARS) 201P
- , Systemic fentanyl enhances the spread of spinal analgesia produced by lignocaine, FASSOULAKI, A., *et al.* 437-439
- Analgesics opioid, morphine**, Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac, BURNS, J. W., *et al.* 235-238
- , Effect of cisapride on morphine absorption after oral administration of sustained-release morphine, ROWBOTHAM, D. J., *et al.* 421-425
- , Gastric emptying and small bowel transit in male volunteers after i.m. ketorolac and morphine, YEE, M. K., *et al.* 426-431
- , Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanose and strychnine, AL-MUHANDIS, W. M., *et al.* 608-613
- , Physiological disposition of i.v. morphine in sheep, SLOAN, P. A., *et al.* 378-386
- , Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice, STOTT, D. G., *et al.* 603-607
- , Speed of onset of analgesia of diamorphine or morphine, SHELLY, M. P., *et al.*, (C) 666
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, DAVIS, C. L., (C) 362-363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, HANNA, M. H., (C) 363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, JOEL, P., (C) 363
- Analgesics opioid, morphine-6-glucuronide**, Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, DAVIS, C. L., (C) 362-363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, HANNA, M. H., (C) 363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, JOEL, P., (C) 363
- Analgesics opioid, papaveretum**, Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704-711
- Analgesics opioid, pethidine**, Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanose and strychnine, AL-MUHANDIS, W. M., *et al.* 608-613
- Analgesics opioid, sufentanil**, Comparison of sufentanil-nitrous oxide anaesthesia with fentanyl-nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery, KIETZMANN, D., *et al.* 269-276
- , Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice, STOTT, D. G., *et al.* 603-607
- Anatomy, chest wall**, A rapid method to assess chest wall shape and volume change, DRUMMOND, G. B., *et al.*, (ARS) 204P
- Antacids, ranitidine**, Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine, ROWBOTHAM, D. J., *et al.* 302-305
- Antagonists benzodiazepine, flumazenil**, Antagonism of benzodiazepine sedation with flumazenil, McCLOY, R., *et al.*, (C) 504
- , Antagonism of benzodiazepine sedation with flumazenil, SANDERS, L., *et al.*, (C) 504
- , Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy, KNUDSEN, L., *et al.* 277-280
- Antagonists glycine**, Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanose and strychnine, AL-MUHANDIS, W. M., *et al.* 608-613
- Antagonists neuromuscular block, 4-aminopyridine**, Investigation of fade in suxamethonium-induced phase II block in the isolated rat diaphragm, GUPTA, V. L., *et al.*, (ARS) 211P
- Antagonists neuromuscular block, edrophonium**, Antagonism of intense atracurium-induced neuromuscular block in children, GWINNUTT, C. L., *et al.* 13-16
- Antagonists neuromuscular block, neostigmine**, Antagonism of intense atracurium-induced neuromuscular block in children, GWINNUTT, C. L., *et al.* 13-16
- , Dose requirements of neostigmine for antagonism of vecuronium neuromuscular block in the elderly: comparison with adults, MCCARTHY, G., *et al.*, (ARS) 652-653P
- , Investigation of fade in suxamethonium-induced phase II block in the isolated rat diaphragm, GUPTA, V. L., *et al.*, (ARS) 211P
- Antagonists opioid, naloxone**, Systemic fentanyl enhances the spread of spinal analgesia produced by lignocaine, FASSOULAKI, A., *et al.* 437-439
- Antibiotics, A23187**, *In vitro* contracture with the calcium ionophore A23187 in skeletal muscle from malignant hyperthermia susceptible and normal individuals, HOPKINS, P. M., *et al.*, (ARS) 202P
- Antibiotics, erythromycin**, Midazolam and erythromycin, WOOD, M., (C) 131
- Arterial pressure**, Arterial pressure responses induced by stimuli to the upper airway in anaesthetized patients, READ, J. R. M., *et al.*, (ARS) 216P

- , Comparison of invasive and non-invasive measurement of continuous arterial pressure using the Finapres, STOKES, D. N., *et al.* 26–35
- , Comparison of the Finapres and direct arterial pressure monitoring during profound hypotensive anaesthesia, AITKEN, H. A., *et al.* 36–40
- , Systolic arterial pressure as a monitor of depth of anaesthesia, ASBURY, A. J., (C) 506
- , Systolic arterial pressure as a monitor of depth of anaesthesia, COUTO DA SILVA, J. M., (C) 506
- Arterial pressure, drug effects**, Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section, ASHTON, W. B., *et al.* 741–747
- , Propofol induces the production of endothelium-derived relaxing factor, PETROS, A. J., *et al.*, (ARS) 645–646P
- Arterial pressure, hypertension**, Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section, ASHTON, W. B., *et al.* 741–747
- , Effects of adenosine triphosphate on the cardiovascular response to tracheal intubation, MIKAWA, K., *et al.* 410–415
- Arterial pressure, measurement**, A new optical transducer for arterial pressure measurement, HACKMAN, C. H., *et al.* 346–352
- , Comparison of invasive and non-invasive measurement of continuous arterial pressure using the Finapres, STOKES, D. N., *et al.* 26–35
- , Comparison of the Finapres and direct arterial pressure monitoring during profound hypotensive anaesthesia, AITKEN, H. A., *et al.* 36–40
- Arteries, cerebral, aneurysm**, Controlled hypotension for cerebral aneurysm surgery in the presence of severe aortic coarctation, GOODIE, D. B., *et al.* 329–331
- Arteries, damage**, Intra-arterial thiopentone is directly toxic to vascular endothelium, MACPHERSON, R. D., *et al.* 546–552
- Basic Physics and Measurement in Anaesthesia*, 3rd Edn, PARBROOK, G. D., *et al.*, (editors), (R) 230
- Bioretransformation (drug)**, Drug bioretransformation by the kidney: how important is it, and how much do we really know? SEAR, J. W., (E) 369–372
- Bioretransformation (drug), bupivacaine**, First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model, PALAZZO, M. G. A., *et al.* 759–763
- Bioretransformation (drug), ketamine**, Pharmacokinetics and distribution of ketamine after extradural administration to dogs, PEDRAZ, J. L., *et al.* 310–316
- Blood, anaesthetic concentration**, Comparison of arterial and arterialized venous concentrations of propofol during infusion of propofol, OKELL, R. W., *et al.* 285–288
- , Hyperventilation and blood concentrations of propofol during total i.v. anaesthesia, ENEVER, G., *et al.*, (ARS) 217–218P
- , Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block, PIHLAJAMÄKI, K. K. 621–622
- , Preliminary study to assay plasma amethocaine concentrations after topical application of a new local anaesthetic cream containing amethocaine, MAZUMDAR, B., *et al.* 432–436
- Blood, erythrocytes**, Malignant hyperthermia: a generalized abnormality of membrane fluidity? COOPER, P., *et al.*, (ARS) 201–202P
- Blood, flow, feto-uteroplacental**, Assessment of the placental circulation, MOORE, J., (E) 671–673
- , Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the feto-placental unit during elective Caesarean section, McLINTIC, A. J., *et al.* 683–689
- , Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms, TURNER, G. A., *et al.* 306–309
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678–682
- Blood, flow, umbilical**, Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms, TURNER, G. A., *et al.* 306–309
- Blood, haemofiltration**, Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration, SHERRER, E. S., *et al.* 569–573
- Blood, loss**, Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty, SHARROCK, N. E., *et al.* 17–25
- Blood, lymphocytes**, Comparison of the effects of anaesthetic agents on mitogen-induced lymphocyte proliferation *in vitro*, O'DONNELL, C. A., *et al.*, (ARS) 658–659P
- Blood, neutrophils**, Comparison of the effects of propofol, midazolam and thiopentone on neutrophil polarization *in vitro*, O'DONNELL, N. G., *et al.*, (ARS) 661P
- Blood, transfusion**, Inappropriate heparinization with a cell saver, COLUMB, M. O., (C) 223
- Blood, volume**, Fluids for resuscitation, VINCENT, J.-L. 185–193
- , Influence of hypertonic volume replacement on the microcirculation in cardiac surgery, BOLDT, J., *et al.* 595–602
- Book Reviews**
- A Colour Atlas of Dental Analgesia and Sedation*, ROBERTS, G. J., *et al.*, (R) 364
- A Pocket Book of Intensive Care: Data, Drugs and Procedures*, 2nd Edn, TINKER, J., *et al.*, (editors), (R) 669
- Advances in Anaesthesia*, Vol. 7, STOELTING, R. K., *et al.*, (editors), (R) 229
- Ambulatory Anaesthesia and Sedation. Impairment and Recovery*, KLEPPER, I. D., *et al.*, (editors), (R) 668
- Anaesthesia*, 3rd Edn, MILLER, R. G., (editor), (R) 364
- Anaesthesia for Ambulatory Surgery*, 2nd Edn, WETCHLER, B. V., (editor), (R) 229–230
- Basic Physics and Measurement in Anaesthesia*, 3rd Edn, PARBROOK, G. D., *et al.*, (editors), (R) 230
- ECG Essentials—A Pocket Reference for Systematic Interpretation*, MURPHY, K. R., *et al.*, (R) 364–365
- Emergency Drug Therapy*, 1st Edn, BARSAN, W. G., *et al.*, (editors), (R) 508–509
- Epidural and Spinal Blockade in Obstetrics*, REYNOLDS, F., (editor), (R) 229
- Gas Monitoring and Pulse Oximetry*, GRAVENSTEIN, J. S., (R) 230
- Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 8th Edn, GILMAN, A. G., *et al.*, (editors), (R) 133
- Handbook of Obstetric Anaesthesia*, BUCHAN, A. S., *et al.*, (R) 509
- Intraoperative Use of Echocardiography* (A Society of Cardiovascular Anesthesiologists Monograph), DEBRUIJN, N. P., *et al.*, (editors), (R) 668–669
- Medical Statistics on Microcomputers*, 1st Edn, BROWN, R. A., *et al.*, (R) 132–133
- Postanaesthetic Care*, FROST, E. A. M., *et al.*, (editors), (R) 133
- Regional Anaesthesia*, 2nd Edn, KOERSTER, W., *et al.*, (editors), (R) 668

- Regional Anaesthesia in Children*, 1st Edn, SAINT-MAURICE, C., *et al.*, (editors), (R) 132
- The Anaesthetic Plan: From Physiologic Principles to Clinical Strategies*, MURAVCHICK, S., (R) 365
- The Lung—Scientific Foundations*, CRYSTAL, R. G., *et al.*, (editors), (R) 230
- Towards a New Pharmacotherapy of Pain*, BASBAUM, A. I., *et al.*, (editors), (R) 805
- Trauma Anesthesia*, STERN, J. K., *et al.*, (editors), (R) 508
- Brain, blood flow**, Effect of P_{aCO_2} on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat, YOUNG, W. L., *et al.* 440–446
- , Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy, KNUDSEN, L., *et al.* 277–280
- Brain, evoked potentials**, Changes in amplitude and latency of the P300 component of the auditory evoked potential with sedative and anaesthetic concentrations of nitrous oxide, JESSOP, J., *et al.* 524–531
- Brain, intracranial neoplasm**, Management of labour and delivery in patients with intracranial neoplasms, FINFER, S. R. 784–787
- Brain, ischaemia**, Transient ischaemic attack after spinal anaesthesia, CHUNG, R. A., *et al.* 635–637
- Brain, oxygen consumption**, Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy, KNUDSEN, L., *et al.* 277–280
- Brain, saccadic eye movements**, Effect of 5% and 10% MAC of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.*, (ARS) 212–213P
- , Effects of low concentrations of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.* 735–740
- Burns**, Pharmacokinetics of alfentanil in burns patients, MACFIE, A. G., *et al.*, (ARS) 657P
- Cancer**, Relationship of postoperative and cancer chemotherapy sickness, DUNDEE, J. W., *et al.*, (ARS) 214P
- , Resistance to atracurium in a patient with an increase in plasma alpha₁ globulins, TATMAN, A. J., *et al.* 623–625
- , Unusual presentation of acute upper airway obstruction caused by an anterior mediastinal mass, AKHTAR, T. M., *et al.* 632–634
- Carbon dioxide, exogenous**, Inhalation induction of anaesthesia with isoflurane: effect of added carbon dioxide, COLEMAN, S. A., *et al.* 257–261
- Carbon dioxide, extracorporeal removal**, Femoral arteriovenous extracorporeal removal of carbon dioxide using a hollow fibre membrane lung, YOUNG, J. D., *et al.*, (ARS) 209P
- , Pressure–volume hysteresis of the lungs in respiratory distress syndrome, RATCLIFFE, F. M., *et al.*, (ARS) 203–204P
- Carbon dioxide, hypocapnia**, Effect of P_{aCO_2} on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat, YOUNG, W. L., *et al.* 440–446
- , Nitrous oxide sedation causes post-hyperventilation apnoea, NORTHWOOD, D., *et al.* 7–12
- Carbon dioxide, measurement**, Measurement of energy expenditure in critical illness using ^{13}C labelled bicarbonate, DEVLIN, J. C., *et al.*, (ARS) 651P
- Carbon dioxide, partial pressure**, Effect of P_{aCO_2} on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat, YOUNG, W. L., *et al.* 440–446
- Cardiorespiratory system, effects**, Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam, PATTERSON, K. W., *et al.* 108–111
- Cardiovascular system, effects**, Cardiovascular effects and regional clearances of i.v. bupivacaine in sheep: enantiomeric analysis, RUTTEN, A. J., *et al.* 247–256
- , Comparative effects of pipecuronium and tubocurarine on plasma concentrations of histamine in humans, NAGUIB, M., *et al.* 320–322
- Cardiovascular system, responses**, Comparison of sufentanil–nitrous oxide anaesthesia with fentanyl–nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery, KIETZMANN, D., *et al.* 269–276
- , Effects of adenosine triphosphate on the cardiovascular response to tracheal intubation, MIKAWA, K., *et al.* 410–415
- , Effects of pindolol on the cardiovascular response to tracheal intubation, MIKAWA, K., *et al.* 416–420
- , Haemodynamic and oxygen transport effects of isoflurane as sedation in ventilated patients in the intensive care unit, BROWNE, G. P. R., *et al.*, (ARS) 652P
- , Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen, REEDER, M. K., *et al.* 326–328
- Cerebrospinal fluid**, Pharmacokinetics and distribution of ketamine after extradural administration to dogs, PEDRAZ, J. L., *et al.* 310–316
- Chemotherapy, cancer**, Relationship of postoperative and cancer chemotherapy sickness, DUNDEE, J. W., *et al.*, (ARS) 214P
- Chick**, Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick, MCLOUGHLIN, C., *et al.* 764–767
- Children**, Antagonism of intense atracurium-induced neuromuscular block in children, GWINNUTT, C. L., *et al.* 13–16
- , Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia, NAITO, Y., *et al.* 387–389
- , Computerized analysis of continuous pulse oximetry in children with nocturnal breathing disorders, WHEATLEY, R. G., *et al.*, (ARS) 208P
- , Cuffed tracheal tubes for paediatric cardiac surgery cause a low incidence of postoperative airway problems, MALMROS, C., *et al.*, (ARS) 655P
- , Diprivan intensive care sedation in children, RODGERS, E. M., (C) 505
- , Dose requirements of atracurium in paediatric intensive care patients, KUSHIMO, O. T., *et al.* 781–783
- , Effect of P6 acupuncture on postoperative vomiting in children undergoing outpatient strabismus correction, LEWIS, I. H., *et al.* 73–78
- , Fresh gas requirement of the Bain system, MEAKIN, G., (C) 663–664
- , Fresh gas requirement of the Bain system, MILLER, D., (C) 664
- , Inhalation induction of anaesthesia with isoflurane: effect of added carbon dioxide, COLEMAN, S. A., *et al.* 257–261
- , Inhalation induction of anaesthesia with isoflurane in children, LEWIS, I. H., (C) 500
- , Inhalation induction of anaesthesia with isoflurane in children, WARDE, D. J., *et al.*, (C) 500–501
- , Ketamine for caudal analgesia in children: comparison with caudal bupivacaine, NAGUIB, M., *et al.* 559–564
- , P6 acupuncture and postoperative vomiting after tonsillectomy in children, YENTIS, S. M., *et al.* 779–780
- , Pharmacokinetic model driven infusion of propofol in children, MARSH, B., *et al.* 41–48
- , Potency and ease of antagonism of pipecuronium in children, LEUWER, M., *et al.*, (ARS) 206–207P

- , Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine, WENSTONE, R., *et al.* 591–594
- , Resting energy expenditure in children with liver disease, WILSON, S. R., *et al.*, (ARS) 216–217P
- Complications, anaphylaxis**, General anaesthetics induce only histamine release selectively from human mast cells, STELLATO, C., *et al.* 751–758
- Complications, anephric patient**, Use of mivacurium chloride by constant infusion in the anephric patient, PHILLIPS, B. J., *et al.*, (ARS) 653–654P
- Complications, aneurysm**, Backache after extradural anaesthesia in the postpartum period: dissection of thoracic aneurysm, KAO, Y. J., *et al.* 335–338
- Complications, aortic coarctation**, Controlled hypotension for cerebral aneurysm surgery in the presence of severe aortic coarctation, GOODIE, D. B., *et al.* 329–331
- Complications, aortic valve disease**, Controlled hypotension for cerebral aneurysm surgery in the presence of severe aortic coarctation, GOODIE, D. B., *et al.* 329–331
- Complications, apnoea**, Computerized analysis of continuous pulse oximetry in children with nocturnal breathing disorders, WHEATLEY, R. G., *et al.*, (ARS) 208P
- , Nitrous oxide sedation causes post-hyperventilation apnoea, NORTHWOOD, D., *et al.* 7–12
- , Pressure-volume hysteresis of the lungs in respiratory distress syndrome, RATCLIFFE, F. M., *et al.*, (ARS) 203–204P
- Complications, arthritis**, Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block, PIHLAJAMÄKI, K. K. 621–622
- Complications, backache**, Backache after extradural anaesthesia in the postpartum period: dissection of thoracic aneurysm, KAO, Y. J., *et al.* 335–338
- Complications, cancer**, Resistance to atracurium in a patient with an increase in plasma α_1 globulins, TATMAN, A. J., *et al.* 623–625
- , Unusual presentation of acute upper airway obstruction caused by an anterior mediastinal mass, AKHTAR, T. M., *et al.* 632–634
- Complications, cardiac arrest**, Calcium for resuscitation? ERDMANN, E., *et al.* 178–184
- , Indications for use of bicarbonate in patients with metabolic acidosis, ARIEFF, A. I. 165–177
- , Resuscitation training for the operating department, BROWN, R. W., *et al.*, (ARS) 219–220P
- Complications, catheter misplacement**, Unsuspected extradural catheterization in an interscalene block, COOK, L. B. 473–475
- Complications, cerebral ischaemia**, Transient ischaemic attack after spinal anaesthesia, CHUNG, R. A., *et al.* 635–637
- Complications, compartment syndrome**, Compartment syndrome after pressurized infusion, TOBIAS, M. D., *et al.* 332–334
- Complications, congenital agranulocytosis**, Anaesthesia and bone marrow aplasia, FENNER, S. G., *et al.*, (C) 665
- , Anaesthesia and bone marrow aplasia, HAMILTON, W. K., (C) 665
- Complications, convulsions**, Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanum and strychnine, AL-MUHANDIS, W. M., *et al.* 608–613
- Complications, death**, Reporting of deaths, LUNN, J., (C) 503
- Complications, drug resistance**, Resistance to atracurium in a patient with an increase in plasma α_1 globulins, TATMAN, A. J., *et al.* 623–625
- , Resistance to non-depolarizing neuromuscular blocking agents, HUNTER, J. M., (E) 511–514
- Complications, eclampsia**, Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section, ASHTON, W. B., *et al.* 741–747
- Complications, haematoma**, Extradural haematoma after continuous extradural anaesthesia, TEKKOK, I. H., *et al.* 112–115
- , Headache after spinal anaesthesia, REID, J. A., *et al.*, (E) 674–677
- Complications, haemorrhage**, Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities, DAVIES, K. R., *et al.* 58–63
- Complications, head injury**, Comparison of thiopentone and propofol at two rates of administration in patients with severe head injury, ANDREWS, P. J. D., *et al.*, (ARS) 212P
- , Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor, ANDREWS, P. J. D., *et al.* 553–558
- Complications, headache**, 29-Gauge spinal needles, LYONS, G., *et al.*, (C) 222
- , Headache after continuous spinal anaesthesia, KESTIN, I. G., (C) 131
- , Headache after continuous spinal anaesthesia, MILLIGAN, H. R., *et al.*, (C) 131
- , Headache after spinal anaesthesia, REID, J. A., *et al.*, (E) 674–677
- , Use of a 25-gauge Whitacre needle to reduce the incidence of postdural puncture headache, LYNCH, J., *et al.* 690–693
- Complications, hepatic**, Halothane hepatitis, RAY, D. C., *et al.* 84–99
- , Screening for antibodies associated with halothane hepatitis, HASTINGS, K. L., *et al.* 722–728
- Complications, hypertension**, Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section, ASHTON, W. B., *et al.* 741–747
- , Effects of adenosine triphosphate on the cardiovascular response to tracheal intubation, MIKAWA, K., *et al.* 410–415
- , Effects of pindolol on the cardiovascular response to tracheal intubation, MIKAWA, K., *et al.* 416–420
- , Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty, SHARROCK, N. E., *et al.* 17–25
- Complications, hyponatraemia**, Dilutional hyponatraemia following transurethral operation for clot retention, HAHN, R. G. 339–340
- , Management of hyponatraemia, SWALES, J. D. 146–153
- Complications, hypotension**, Can glycopyrrolate attenuate propofol-induced hypotension in elderly patients? SNEYD, J. R., *et al.*, (ARS) 661–662P
- , Preanaesthetic medication with clonidine: a dose-response study, CARABINE, U. A., *et al.* 79–83
- Complications, hypoxia**, Nitrous oxide sedation causes post-hyperventilation apnoea, NORTHWOOD, D., *et al.* 7–12
- Complications, intra-arterial injection**, Intra-arterial thiopentone is directly toxic to vascular endothelium, MACPHERSON, R. D., *et al.* 546–552
- Complications, liver disease**, Resting energy expenditure in children with liver disease, WILSON, S. R., *et al.*, (ARS) 216–217P
- Complications, masseter spasm**, Jaw stiffness—an ill understood condition, SADDLER, J. M., (E) 515–516

- Complications, morbidity**, Morbidity following day-case procedures, SMITH, S. O., *et al.*, (ARS) 644-645P
- Complications, myocardial infarction**, Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty, SHARROCK, N. E., *et al.* 17-25
- , Postoperative myocardial ischaemia in patients with recent myocardial infarction, METZLER, H., *et al.* 317-319
- , Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population, MUIR, A. D., *et al.* 373-377
- , Silent myocardial ischaemia in preoperative patients: what does it mean, and what should be done about it? DE BONO, D. P., *et al.*, (E) 367-368
- Complications, myolysis**, Relationship between exercise-induced myolysis and malignant hyperthermia, HACKL, W., *et al.*, (C) 221
- , Relationship between exercise-induced myolysis and malignant hyperthermia, KRIVOSIC-HORBER, R., *et al.*, (C) 221
- Complications, myotonic dystrophy**, Myotonias and susceptibility to malignant hyperthermia, GRONERT, G. A., (C) 221
- , Myotonias and susceptibility to malignant hyperthermia, LEHMANN-HORN, F., *et al.*, (C) 221-222
- Complications, neoplasm**, Management of labour and delivery in patients with intracranial neoplasms, FINFER, S. R. 784-787
- Complications, obesity**, Change in end-expiratory respiratory volume with thiopentone or propofol induction of anaesthesia, RUTHERFORD, J. S., *et al.*, (ARS) 647P
- , Effectiveness of preoxygenation in morbidly obese patients, BERTHOUD, M. C., *et al.* 464-466
- Complications, oedema**, Fluids for resuscitation, VINCENT, J.-L. 185-193
- , Non-cardiogenic pulmonary oedema after transfusion with granulocyte antibody containing blood: treatment with extracorporeal membrane oxygenation, WORSLEY, M. H., *et al.* 116-119
- Complications, oliguria**, Is postoperative oliguria avoidable? SWENY, P. 137-145
- Complications, pacemaker failure**, Interference with pacemaker function, FINFER, S. R., (C) 664-665
- , Interference with pacemaker function, SIDHU, V. S., (C) 664
- Complications, pneumothorax**, Delayed pneumothorax after subclavian vein catheterization and positive pressure ventilation, CRONEN, M. C., *et al.* 480-482
- , Identification of the interpleural space, LEE, E., *et al.*, (C) 130
- , Identification of the interpleural space, SCOTT, P. V., (C) 130
- , Tension pneumothorax—wrong tube? KNEESHAW, J. D., (C) 222-223
- Complications, positional**, The prone position for the surgical patient: a historical review of the principles and hazards, ANDERTON, J. M. 452-463
- Complications, regurgitation**, Gastro-oesophageal reflux and tracheobronchial contamination in the intensive care unit, KIRBY, F., *et al.*, (ARS) 655P
- , Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, BARKER, P., *et al.*, (ARS) 660P
- Complications, respiratory depression**, Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice, STOTT, D. G., *et al.* 603-607
- Complications, thrombosis**, Deep venous thrombosis and anaesthesia, JØRGENSEN, L. N., (C) 128
- , Deep venous thrombosis and anaesthesia, MCKENZIE, P. J., (C) 128
- , Deep venous thrombosis and anaesthesia, MODIG, J., (C) 127-128
- , Deep venous thrombosis and anaesthesia, MODIG, J., (C) 128
- , Superior sagittal sinus thrombosis after internal jugular vein cannulation, STEPHENS, P. H., *et al.* 476-479
- , Venous sequelae after i.v. diclofenac, CAMPBELL, W., *et al.*, (C) 803
- , Venous sequelae after i.v. diclofenac, GOPINATH, R., (C) 803
- Complications, transplants**, Anaesthesia for patients with transplanted hearts and lungs undergoing non-cardiac surgery, SHAW, I. H., *et al.* 772-778
- Developing country**, Anaesthetic equipment for a developing country, PEDERSEN, J., (C) 360
- , Anaesthetic equipment for a developing country, TIGHE, S. Q. M., (C) 360
- Dog**, Pharmacokinetics and distribution of ketamine after extradural administration to dogs, PEDRAZ, J. L., *et al.* 310-316
- Drug delivery, buccal**, Use of buccal prochlorperazine in the prevention of postoperative sickness, PATTERSON, K. W., *et al.*, (ARS) 213-214P
- Drug delivery, computerized**, Pharmacokinetic model driven infusion of propofol in children, MARSH, B., *et al.* 41-48
- , Sedation with propofol during surgery under regional block: evaluation of a computer controlled infusion system, SKIPSEY, I. G., *et al.*, (ARS) 218-219P
- Drug delivery, oral**, Effect of cisapride on morphine absorption after oral administration of sustained-release morphine, ROWBOTHAM, D. J., *et al.* 421-425
- , Investigation of the effect of oral diazepam on upper airway reactivity, MURPHY, P. J., *et al.*, (ARS) 660-661P
- Drug delivery, sublingual**, Effect of sublingual buprenorphine on gastric emptying of a liquid meal, TROTTER, T. N., *et al.* 748-750
- ECG Essentials—A Pocket Reference for Systematic Interpretation*, MURPHY, K. R., *et al.*, (R) 364-365
- Education, medical students**, Resuscitation training for the operating department, BROWN, R. W., *et al.*, (ARS) 219-220P
- Emergency Drug Therapy*, 1st Edn, BARSAN, W. G., *et al.*, (editors), (R) 508-509
- Enzymes, creatine kinase**, Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick, McLOUGHLIN, C., *et al.* 764-767
- Epidural and Spinal Blockade in Obstetrics*, REYNOLDS, F., (editor), (R) 229
- Equipment, alarms**, AURA: a new respiratory monitor and apnoea alarm for spontaneously breathing patients, CYNIA, A. M., *et al.* 341-345
- Equipment, anaesthesia machines**, Anaesthetic equipment for a developing country, PEDERSEN, J., (C) 360
- , Anaesthetic equipment for a developing country, TIGHE, S. Q. M., (C) 360
- Equipment, breathing systems**, Fresh gas requirement of the Bain system, MEAKIN, G., (C) 663-664
- , Fresh gas requirement of the Bain system, MILLER, D., (C) 664
- , Fresh gas utilization of eight circle systems, ZBINDEN, A. M., *et al.* 492-499
- , Preoxygenation: use of a high flow delivery system, OOI, R., *et al.*, (ARS) 208P

- Equipment, computers**, A system for automatic feedback control of plasma potassium concentration, HEINING, M. P. D., *et al.* 120-126
- , Pharmacokinetic model driven infusion of propofol in children, MARSH, B., *et al.* 41-48
- Equipment, cuffs tracheal**, Cuffed tracheal tubes for paediatric cardiac surgery cause a low incidence of postoperative airway problems, MALMROS, C., *et al.*, (ARS) 655P
- , Gastro-oesophageal reflux and tracheobronchial contamination in the intensive care unit, KIRBY, F., *et al.*, (ARS) 655P
- Equipment, Finapres**, Comparison of invasive and non-invasive measurement of continuous arterial pressure using the Finapres, STOKES, D. N., *et al.* 26-35
- , Comparison of the Finapres and direct arterial pressure monitoring during profound hypotensive anaesthesia, AITKEN, H. A., *et al.* 36-40
- Equipment, gas analysers**, Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor, ANDREWS, P. J. D., *et al.* 553-558
- Equipment, Guedel airway**, Airway obstruction associated with the use of the Guedel airway, MARSH, A. M., *et al.* 517-523
- , Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, BARKER, P., *et al.*, (ARS) 660P
- Equipment, heat-moisture exchangers**, Work of ventilating heat and moisture exchangers, CHUNG, R., *et al.*, (ARS) 647-648P
- Equipment, helicopters**, Transfer of patients by helicopter, BRISTOW, A., (C) 127
- , Transfer of patients by helicopter, DEMELLO, W. F., (C) 127
- Equipment, laryngoscopes**, Analysis of the shape of the laryngoscope blade, MARKS, R. R. D., *et al.*, (ARS) 654P
- Equipment, masks anaesthesia**, Comparison of laryngeal mask airway with tracheal intubation for intraocular surgery, AKHTAR, T. M., *et al.*, (ARS) 215P
- , Desaturation and induction characteristics: comparison of propofol and thiopentone during mask anaesthesia with isoflurane, HEAD-RAPSON, A. G., *et al.*, (ARS) 203P
- , Failed tracheal intubation, KING, T. A., *et al.*, (C) 225
- , Failed tracheal intubation, O'SULLIVAN, G., *et al.*, (C) 225
- , Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, BARKER, P., *et al.*, (ARS) 660P
- , Video surveillance of oxygen administration by mask in postoperative patients, NOLAN, K. M., *et al.*, (ARS) 650-651P
- Equipment, masks surgical**, Regional anaesthesia requires attention to detail, WILDSMITH, J. A. W., (C) 224-225
- Equipment, monitors**, AURA: a new respiratory monitor and apnoea alarm for spontaneously breathing patients, CYNA, A. M., *et al.* 341-345
- Equipment, needles**, 29-Gauge spinal needles, LYONS, G., *et al.*, (C) 222
- , Headache after continuous spinal anaesthesia, KESTIN, I. G., (C) 131
- , Headache after continuous spinal anaesthesia, MILLIGAN, H. R., *et al.*, (C) 131
- , Headache after spinal anaesthesia, REID, J. A., *et al.*, (E) 674-677
- , Spinal needles, COONEY, C., *et al.*, (C) 360-361
- , Use of a 25-gauge Whitacre needle to reduce the incidence of postdural puncture headache, LYNCH, J., *et al.* 690-693
- Equipment, pacemakers**, Interference with pacemaker function, FINFER, S. R., (C) 664-665
- , Interference with pacemaker function, SIDHU, V. S., (C) 664
- Equipment, pulse oximeters**, Response time of finger and ear pulse oximeter probes during hypoxaemic events occurring during anaesthesia, BROOME, I. J., *et al.*, (ARS) 207P
- , Temperature dependence of LED and its theoretical effect on pulse oximetry, REYNOLDS, K. J., *et al.* 638-643
- Equipment, scavenging devices**, Determination of contamination of a chemical warfare-proof operating theatre with volatile anaesthetic agents and assessment of anaesthetic gas scavenging systems, YOGANATHAN, S., *et al.* 614-617
- Equipment, sensors fibreoptic**, Fibreoptic sensors in clinical measurement, YELLOWLEES, I. H. 100-105
- Equipment, silica gel**, Absorption of isoflurane by silica gel, LUMB, A. B., *et al.* 106-107
- Equipment, transducers**, A new optical transducer for arterial pressure measurement, HACKMAN, C. H., *et al.* 346-352
- Equipment, tubes tracheal**, Cuffed tracheal tubes for paediatric cardiac surgery cause a low incidence of postoperative airway problems, MALMROS, C., *et al.*, (ARS) 655P
- Equipment, tubes tracheal, gas injection**, Pressure support ventilation using a new tracheal gas injection tube, BEYDON, L., *et al.* 795-800
- Equipment, ventilators**, Pressure support ventilation using a new tracheal gas injection tube, BEYDON, L., *et al.* 795-800
- , The pneuPAC hyperbaric variant HB: a ventilator suitable for use within a one-man hyperbaric chamber, SPITTAL, M. J., *et al.* 488-491
- , Work of ventilating heat and moisture exchangers, CHUNG, R., *et al.*, (ARS) 647-648P
- Equipment, videos**, Video surveillance of oxygen administration by mask in postoperative patients, NOLAN, K. M., *et al.*, (ARS) 650-651P
- Fetus**, Assessment of the placental circulation, MOORE, J., (E) 671-673
- , Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the foeto-placental unit during elective Caesarean section, MCCLINTIC, A. J., *et al.* 683-689
- , Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms, TURNER, G. A., *et al.* 306-309
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678-682
- Fluid balance**, Fluid and electrolytes revisited, WILLATTS, S. M., (E) 135-136
- , Fluids for resuscitation, VINCENT, J.-L. 185-193
- , Influence of hypertonic volume replacement on the microcirculation in cardiac surgery, BOLDT, J., *et al.* 595-602
- , Is postoperative oliguria avoidable? SWENY, P. 137-145
- , Management of hyponatraemia, SWALES, J. D. 146-153
- , Picolax bowel preparation, DODSON, M. E., (C) 664
- Fluids**, l.v., Compartment syndrome after pressurized infusion, TOBIAS, M. D., *et al.* 332-334
- Formulations, pH**, Comparison of plain and alkalized local anesthetic mixtures of lignocaine and bupivacaine for elective extradural Caesarean section, FERNANDO, R., *et al.* 699-703
- Gas Monitoring and Pulse Oximetry**, GRAVENSTEIN, J. S., (R) 230

- Gastrointestinal tract, bowel function**, Gastric emptying and small bowel transit in male volunteers after i.m. ketorolac and morphine, YEE, M. K., *et al.* 426-431
- , Picolax bowel preparation, DODSON, M. E., (C) 664
- Gastrointestinal tract, emptying**, Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine, ROWBOTHAM, D. J., *et al.* 302-305
- , Effect of sublingual buprenorphine on gastric emptying of a liquid meal, TROTTER, T. N., *et al.* 748-750
- , Gastric emptying and small bowel transit in male volunteers after i.m. ketorolac and morphine, YEE, M. K., *et al.* 426-431
- , Gastric emptying in pregnancy, MACFIE, A. G., *et al.* 54-57
- , Peripartum changes in gastric emptying, SANDHAR, B. K., *et al.*, (ARS) 213P
- Gastrointestinal tract, endoscopy**, Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam, PATTERSON, K. W., *et al.* 108-111
- Gastrointestinal tract, pH**, Gastro-oesophageal reflux and tracheobronchial contamination in the intensive care unit, KIRBY, F., *et al.*, (ARS) 655P
- Gastrointestinal tract, prokinesia, cisapride**, Effect of cisapride on morphine absorption after oral administration of sustained-release morphine, ROWBOTHAM, D. J., *et al.* 421-425
- Gastrointestinal tract, reflux**, Gastro-oesophageal reflux and tracheobronchial contamination in the intensive care unit, KIRBY, F., *et al.*, (ARS) 655P
- , Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway, BARKER, P., *et al.*, (ARS) 660P
- Gastrointestinal tract, stomach antacids**, Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine, ROWBOTHAM, D. J., *et al.* 302-305
- Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 8th Edn, GILMAN, A. G., *et al.*, (editors), (R) 133
- Handbook of Obstetric Anaesthesia*, BUCHAN, A. S., *et al.*, (R) 509
- Head, injury**, Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor, ANDREWS, P. J. D., *et al.* 553-558
- Heart, cardiac massage**, Resuscitation training for the operating department, BROWN, R. W., *et al.*, (ARS) 219-220P
- Heart, cardiac output**, Clinical and haemodynamic effects of milrinone in the treatment of low cardiac output after cardiac surgery, WRIGHT, E. M., *et al.* 585-590
- , Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients, SHARROCK, N. E., *et al.* 694-698
- , Enoximone during coronary bypass surgery, RAFTERY, S., *et al.*, (ARS) 651-652P
- , Non-invasive measurement of cardiac output by thoracic electrical bioimpedance: a study of reproducibility and comparison with thermodilution, JEWKES, C., *et al.* 788-794
- , Non-invasive measurement of cardiac output during induction of anaesthesia and tracheal intubation: thiopentone and propofol compared, VOHRA, A., *et al.* 64-68
- Heart, cardiopulmonary bypass**, Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass, BOER, F., *et al.* 69-72
- , Enoximone during coronary bypass surgery, RAFTERY, S., *et al.*, (ARS) 651-652P
- , Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine, WENSTONE, R., *et al.* 591-594
- Heart, coronary artery bypass**, Enoximone during coronary bypass surgery, RAFTERY, S., *et al.*, (ARS) 651-652P
- , Influence of hypertonic volume replacement on the microcirculation in cardiac surgery, BOLDT, J., *et al.* 595-602
- Heart, coronary occlusion**, Postoperative myocardial ischaemia in patients with recent myocardial infarction, METZLER, H., *et al.* 317-319
- Heart, enoximone**, Enoximone during coronary bypass surgery, RAFTERY, S., *et al.*, (ARS) 651-652P
- Heart, esmolol**, Repair of traumatic transection of the thoracic aorta: esmolol for intraoperative control of arterial pressure, FENNER, S. G., *et al.* 483-487
- Heart, ischaemia**, Postoperative myocardial ischaemia in patients with recent myocardial infarction, METZLER, H., *et al.* 317-319
- , Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia, REEDER, M. K., *et al.* 626-631
- , Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population, MUIR, A. D., *et al.* 373-377
- , Relationship between perioperative ischaemic and hypoxic events in patients with cardiovascular disease, GILL, N., *et al.*, (ARS) 649P
- , Silent myocardial ischaemia in preoperative patients: what does it mean, and what should be done about it? DE BONO, D. P., *et al.*, (E) 367-368
- Heart, milrinone**, Clinical and haemodynamic effects of milrinone in the treatment of low cardiac output after cardiac surgery, WRIGHT, E. M., *et al.* 585-590
- Heart, myocardial function**, Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities, DAVIES, K. R., *et al.* 58-63
- Heart, pacemakers artificial**, Interference with pacemaker function, FINFER, S. R., (C) 664-665
- , Interference with pacemaker function, SIDHU, V. S., (C) 664
- Heart, pindolol**, Effects of pindolol on the cardiovascular response to tracheal intubation, MIKAWA, K., *et al.* 416-420
- Heart, resuscitation**, Calcium for resuscitation? ERDMANN, E., *et al.* 178-184
- , Fluids for resuscitation, VINCENT, J.-L. 185-193
- , Resuscitation training for the operating department, BROWN, R. W., *et al.*, (ARS) 219-220P
- Heart, sodium nitroprusside**, Repair of traumatic transection of the thoracic aorta: esmolol for intraoperative control of arterial pressure, FENNER, S. G., *et al.* 483-487
- Heart, transplantation**, Anaesthesia for patients with transplanted hearts and lungs undergoing non-cardiac surgery, SHAW, I. H., *et al.* 772-778
- Heart, vascular pressures**, Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass, BOER, F., *et al.* 69-72
- , Enoximone during coronary bypass surgery, RAFTERY, S., *et al.*, (ARS) 651-652P
- Heart, ventricles**, Left ventricular function during transoesophageal echocardiographic assessment of abdominal aortic aneurysm resection, RYAN, T., *et al.*, (ARS) 204-205P
- Histamine**, Comparative effects of pipercuronium and tubocurarine on plasma concentrations of histamine in humans, NAGUIB, M., *et al.* 320-322

- , General anaesthetics induce only histamine release selectively from human mast cells, STELLATO, C., *et al.* 751–758
- History, anaesthesia local**, Intra-arterial regional analgesia, AUSTIN, T. R., (C) 803
- , Intra-arterial regional analgesia, GILSANZ, F., (C) 803–804
- , Intra-arterial regional analgesia, KOSCIELNIAK-NIELSEN, Z. J., (C) 804
- History, halothane**, Halothane hepatitis, RAY, D. C., *et al.* 84–99
- History, prone position**, The prone position for the surgical patient: a historical review of the principles and hazards, ANDERTON, J. M. 452–463
- Hormones, aldosterone**, Is postoperative oliguria avoidable? SWENY, P. 137–145
- Hormones, antidiuretic**, Is postoperative oliguria avoidable? SWENY, P. 137–145
- Hormones, cortisol**, Midazolam modifies pancreatic and anterior pituitary hormone secretion during upper abdominal surgery, DESBOROUGH, J. P., *et al.* 390–396
- Hormones, growth**, Midazolam modifies pancreatic and anterior pituitary hormone secretion during upper abdominal surgery, DESBOROUGH, J. P., *et al.* 390–396
- Hormones, insulin**, Midazolam modifies pancreatic and anterior pituitary hormone secretion during upper abdominal surgery, DESBOROUGH, J. P., *et al.* 390–396
- Hormones, responses**, Effects of labetalol on perioperative stress markers and isoflurane requirements, AMAR, D., *et al.* 296–301
- , Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic, CARLI, F., *et al.* 729–734
- Hyperbaria, chamber**, The pneuPAC hyperbaric variant HB: a ventilator suitable for use within a one-man hyperbaric chamber, SPITALL, M. J., *et al.* 488–491
- Hypnotics benzodiazepine, midazolam**, A comparison of dexmedetomidine, an α_1 -adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery, AANTAA, R., *et al.* 402–409
- , Alcohol after sedation with i.v. midazolam-fentanyl: effects on psychomotor functioning, LICHTOR, J. L., *et al.* 579–584
- , Comparison of the effects of anaesthetic agents on mitogen-induced lymphocyte proliferation *in vitro*, O'DONNELL, C. A., *et al.* (ARS) 658–659P
- , Comparison of the effects of propofol, midazolam and thiopentone on neutrophil polarization *in vitro*, O'DONNELL, N. G., *et al.* (ARS) 661P
- , Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy, KNUDSEN, L., *et al.* 277–280
- , Midazolam and erythromycin, WOOD, M., (C) 131
- , Midazolam and propofol for induction of anaesthesia, McCLUNE, S., *et al.* (ARS) 215–216P
- , Midazolam modifies pancreatic and anterior pituitary hormone secretion during upper abdominal surgery, DESBOROUGH, J. P., *et al.* 390–396
- , Propofol and midazolam act synergistically in combination, SHORT, T. G., *et al.* 539–545
- , Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam, PATTERSON, K. W., *et al.* 108–111
- Hypoxaemia**, Computerized analysis of continuous pulse oximetry in children with nocturnal breathing disorders, WHEATLEY, R. G., *et al.* (ARS) 208P
- , Nitrous oxide sedation causes post-hyperventilation apnoea, NORTHWOOD, D., *et al.* 7–12
- , Pain relief and hypoxaemia during administration of extradural fentanyl by three different methods, KLUGER, M. T., *et al.* (ARS) 656–657P
- , Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704–711
- , Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia, REEDER, M. K., *et al.* 626–631
- , Response time of finger and ear pulse oximeter probes during hypoxaemic events occurring during anaesthesia, BROOME, I. J., *et al.* (ARS) 207P
- , Uncertainties about the ventilatory response to hypoxaemia, KNILL, R. L., (C) 223–224
- , Uncertainties about the ventilatory response to hypoxaemia, NUNN, J. F., (C) 224
- Hypoxia**, Indications for use of bicarbonate in patients with metabolic acidosis, ARIEFF, A. I. 165–177
- , Relationship between perioperative ischaemic and hypoxic events in patients with cardiovascular disease, GILL, N., *et al.* (ARS) 649P
- Immune response, anti-TFA antibodies**, Screening for antibodies associated with halothane hepatitis, HASTINGS, K. L., *et al.* 722–728
- Induction, anaesthesia**, Desaturation and induction characteristics: comparison of propofol and thiopentone during mask anaesthesia with isoflurane, HEAD-RAPSON, A. G., *et al.* (ARS) 203P
- , Midazolam and propofol for induction of anaesthesia, McCLUNE, S., *et al.* (ARS) 215–216P
- , Non-invasive measurement of cardiac output during induction of anaesthesia and tracheal intubation: thiopentone and propofol compared, VOHRA, A., *et al.* 64–68
- , Propofol and midazolam act synergistically in combination, SHORT, T. G., *et al.* 539–545
- Induction, anaesthesia, rapid sequence**, Rapid inhalation induction with isoflurane in humidified carrier gas, VAN HEERDEN, P. V., *et al.* 470–472
- Infants**, Potency and ease of antagonism of pipercuronium in children, LEUWER, M., *et al.* (ARS) 206–207P
- , Resting energy expenditure in children with liver disease, WILSON, S. R., *et al.* (ARS) 216–217P
- Infections, bacteria**, Bacterial growth in propofol, McLEOD, G. A., *et al.* (C) 665–666
- Intensive care**, Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration, SHEARER, E. S., *et al.* 569–573
- , Dose requirements of atracurium in paediatric intensive care patients, KUSHIMO, O. T., *et al.* 781–783
- , Gastro-oesophageal reflux and tracheobronchial contamination in the intensive care unit, KIRBY, F., *et al.* (ARS) 655P
- Intensive care, sedation**, Does physiotherapy affect the auditory evoked potentials of sedated patients in the intensive care unit? SNEYD, J. R., *et al.* (ARS) 647P
- , Haemodynamic and oxygen transport effects of isoflurane as sedation in ventilated patients in the intensive care unit, BROWNE, G. P. R., *et al.* (ARS) 652P
- Interactions (drug)**, Alcohol after sedation with i.v. midazolam-fentanyl: effects on psychomotor functioning, LICHTOR, J. L., *et al.* 579–584
- , Atracurium and suxamethonium, DONATI, F., (C) 502
- , Atracurium and suxamethonium, FAUVEL, N. J., *et al.* (C) 502
- , Determinants of antagonism of non-depolarizing neuromuscular block, BEEMER, G. H., *et al.* (C) 362
- , Determinants of antagonism of non-depolarizing neuromuscular block, CAMPBELL, J. R., (C) 362
- , Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine, ROWBOTHAM, D. J., *et al.* 302–305
- , Interaction between betamethasone and vecuronium, PARR, S. M., *et al.* 447–451
- , Midazolam and erythromycin, WOOD, M., (C) 131

- , Midazolam and propofol for induction of anaesthesia, *McCLUNE, S., et al.*, (ARS) 215-216P
- , Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick, *McLOUGHLIN, C., et al.* 764-767
- , Propofol and midazolam act synergistically in combination, *SHORT, T. G., et al.* 539-545
- , Synergism among i.v. anaesthetics, *McKAY, A. C., et al.* 1-3
- , Thiopentone-propofol hypnotic synergism in patients, *NAGUIB, M., et al.* 4-6
- Intraoperative Use of Echocardiography** (A Society of Cardiovascular Anesthesiologists Monograph), *DEBRUIJN, N. P., et al.*, (editors), (R) 668-669
- Intubation tracheal**, Comparison of laryngeal mask airway with tracheal intubation for intraocular surgery, *AKHTAR, T. M., et al.*, (ARS) 215P
- , Gastro-oesophageal reflux and tracheobronchial contamination in the intensive care unit, *KIRBY, F., et al.*, (ARS) 655P
- Intubation tracheal, complications**, Failed tracheal intubation, *KING, T. A., et al.*, (C) 225
- , Failed tracheal intubation, *O'SULLIVAN, G., et al.*, (C) 225
- Intubation tracheal, difficult**, Predicting difficult intubation, *BELLHOUSE, P.*, (C) 505
- , Predicting difficult intubation, *OATES, J. D. L., et al.*, (C) 505
- , Tracheal intubation with the patient in a sitting position, *BROCK-UTNE, J. G., et al.*, (C) 225-226
- , Unexpected, difficult laryngoscopy, *BELLHOUSE, P.*, (C) 501
- , Unexpected, difficult laryngoscopy, *CORMACK, R. R., et al.*, (C) 501-502
- Intubation tracheal, responses**, Arterial pressure responses induced by stimuli to the upper airway in anesthetized patients, *READ, J. R. M., et al.*, (ARS) 216P
- , Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section, *ASHTON, W. B., et al.* 741-747
- , Effects of adenosine triphosphate on the cardiovascular response to tracheal intubation, *MIKAWA, K., et al.* 410-415
- , Effects of pindolol on the cardiovascular response to tracheal intubation, *MIKAWA, K., et al.* 416-420
- , Non-invasive measurement of cardiac output during induction of anaesthesia and tracheal intubation: thiopentone and propofol compared, *VOHRA, A., et al.* 64-68
- Intubation tracheal, techniques**, Tracheal intubation with the patient in a sitting position, *BROCK-UTNE, J. G., et al.*, (C) 225-226
- , Tracheal intubation with the patient in the sitting position, *ADAMS, A. K., et al.* 804
- Intubation tracheal, training**, Training in fiberoptic laryngoscopy, *BRIMACOMBE, J.*, (C) 503
- , Training in fiberoptic laryngoscopy, *TELFORD, R. J., et al.*, (C) 503
- Ions, calcium**, Calcium for resuscitation? *ERDMANN, E., et al.* 178-184
- Ions, chloride**, Is postoperative oliguria avoidable? *SWENY, P.* 137-145
- Ions, potassium**, A system for automatic feedback control of plasma potassium concentration, *HEINING, M. P. D., et al.* 120-126
- , Potassium in the perioperative period, *VAUGHAN, R. S.* 194-200
- Ions, sodium**, Is postoperative oliguria avoidable? *SWENY, P.* 137-145
- , Management of hyponatraemia, *SWALES, J. D.* 146-153
- Kidney, anephric patient**, Use of mivacurium chloride by constant infusion in the anephric patient, *PHILLIPS, B. J., et al.*, (ARS) 653-654P
- Kidney, failure**, Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration, *SHEARER, E. S., et al.* 569-573
- Kidney, function**, Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration, *SHEARER, E. S., et al.* 569-573
- , Is postoperative oliguria avoidable? *SWENY, P.* 137-145
- , Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine, *WENSTONE, R., et al.* 591-594
- , Roles of the liver and kidney in acid-base regulation and its disorders, *COHEN, R. D.* 154-164
- Kidney, metabolism**, Drug biotransformation by the kidney: how important is it, and how much do we really know? *SEAR, J. W., et al.* 369-372
- , Physiological disposition of i.v. morphine in sheep, *SLOAN, P. A., et al.* 378-386
- Kidney, urine**, Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration, *SHEARER, E. S., et al.* 569-573
- , Is postoperative oliguria avoidable? *SWENY, P.* 137-145
- , Roles of the liver and kidney in acid-base regulation and its disorders, *COHEN, R. D.* 154-164
- Larynx, laryngoscopy**, Training in fiberoptic laryngoscopy, *BRIMACOMBE, J.*, (C) 503
- , Training in fiberoptic laryngoscopy, *TELFORD, R. J., et al.*, (C) 503
- , Unexpected, difficult laryngoscopy, *BELLHOUSE, P.*, (C) 501
- , Unexpected, difficult laryngoscopy, *CORMACK, R. R., et al.*, (C) 501-502
- Liver, hepatitis**, Halothane hepatitis, *RAY, D. C., et al.* 84-99
- , Screening for antibodies associated with halothane hepatitis, *HASTINGS, K. L., et al.* 722-728
- Liver, hepatotoxicity**, Halothane hepatitis, *RAY, D. C., et al.* 84-99
- Liver, metabolism**, Physiological disposition of i.v. morphine in sheep, *SLOAN, P. A., et al.* 378-386
- , Roles of the liver and kidney in acid-base regulation and its disorders, *COHEN, R. D.* 154-164
- Lung, damage**, Direct evidence for free radical generation in experimental lung injury, *MURPHY, P. G., et al.*, (ARS) 649-650P
- Lung, interpleural space**, Identification of the interpleural space, *LEE, E., et al.*, (C) 130
- , Identification of the interpleural space, *SCOTT, P. V., et al.*, (C) 130
- Lung, model**, Femoral arteriovenous extracorporeal removal of carbon dioxide using a hollow fibre membrane lung, *YOUNG, J. D., et al.*, (ARS) 209P
- , First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model, *PALAZZO, M. G. A., et al.* 759-763
- Lung, pneumothorax**, Identification of the interpleural space, *LEE, E., et al.*, (C) 130
- , Identification of the interpleural space, *SCOTT, P. V., et al.*, (C) 130
- Lung, respiratory distress syndrome**, Pressure-volume hysteresis of the lungs in respiratory distress syndrome, *RATCLIFFE, F. M., et al.*, (ARS) 203-204P
- Lung, transplantation**, Anaesthesia for patients with

- transplanted hearts and lungs undergoing non-cardiac surgery, SHAW, I. H., *et al.* 772-778
- Lung, volume,** Change in end-expiratory respiratory volume with thiopentone or propofol induction of anaesthesia, RUTHERFORD, J. S., *et al.*, (ARS) 647P
- , Pressure-volume hysteresis of the lungs in respiratory distress syndrome, RATCLIFFE, F. M., *et al.*, (ARS) 203-204P
- Malignant hyperthermia,** *In vitro* contracture with the calcium ionophore A23187 in skeletal muscle from malignant hyperthermia susceptible and normal individuals, HOPKINS, P. M., *et al.*, (ARS) 202P
- , Malignant hyperthermia: a generalized abnormality of membrane fluidity? COOPER, P., *et al.*, (ARS) 201-202P
- , Myotonias and susceptibility to malignant hyperthermia, GRONERT, G. A., (C) 221
- , Myotonias and susceptibility to malignant hyperthermia, LHMANN-HORN, F., *et al.*, (C) 221-222
- , Relationship between exercise-induced myolysis and malignant hyperthermia, HACKL, W., *et al.*, (C) 221
- , Relationship between exercise-induced myolysis and malignant hyperthermia, KRIVOSIC-HORBER, R., *et al.*, (C) 221
- Measurement techniques, acoustic reflection,** Improved method of acoustic reflection technique for upper airway measurements, MARAN, N. J., *et al.*, (ARS) 648P
- Measurement techniques, airway reactivity,** A portable method to assess upper airway reactivity, LANGTON, J., *et al.*, (ARS) 648-649P
- Measurement techniques, applied potential tomography,** Effect of sublingual buprenorphine on gastric emptying of a liquid meal, TROTTER, T. N., *et al.* 748-750
- , Peripartum changes in gastric emptying, SANDHAR, B. K., *et al.*, (ARS) 213P
- Measurement techniques, arterial pressure,** A new optical transducer for arterial pressure measurement, HACKMAN, C. H., *et al.* 346-352
- , Comparison of invasive and non-invasive measurement of continuous arterial pressure using the Finapres, STOKES, D. N., *et al.* 26-35
- , Comparison of the Finapres and direct arterial pressure monitoring during profound hypotensive anaesthesia, ATKEN, H. A., *et al.* 36-40
- Measurement techniques, blood flow, placenta,** Assessment of the placental circulation, MOORE, J., (E) 671-673
- , Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms, TURNER, G. A., *et al.* 306-309
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678-682
- Measurement techniques, contracture test for MH,** *In vitro* contracture with the calcium ionophore A23187 in skeletal muscle from malignant hyperthermia susceptible and normal individuals, HOPKINS, P. M., *et al.*, (ARS) 202P
- Measurement techniques, Doppler ultrasound,** Assessment of the placental circulation, MOORE, J., (E) 671-673
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678-682
- , Haemodynamic effects of propofol: induction with 2.5 mg kg⁻¹, FAIRFIELD, J. E., *et al.* 618-620
- Measurement techniques, drug concentration,** Comparison of arterial and arterialized venous concentrations of propofol during infusion of propofol, OKELL, R. W., *et al.* 285-288
- Measurement techniques, electromyography,** Spectral analysis of the electromyogram: effect of fentanyl, SEVERN, A. M., *et al.*, (ARS) 650P
- Measurement techniques, electron spin resonance,** Direct evidence for free radical generation in experimental lung injury, MURPHY, P. G., *et al.*, (ARS) 649-650P
- Measurement techniques, energy expenditure,** Measurement of energy expenditure in critical illness using ¹³C labelled bicarbonate, DEVLIN, J. C., *et al.*, (ARS) 651P
- Measurement techniques, fiberoptic,** Fiberoptic sensors in clinical measurement, YELLOWLEES, I. H. 100-105
- Measurement techniques, flow velocity waveform analysis,** Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms, TURNER, G. A., *et al.* 306-309
- Measurement techniques, MUGA scan,** Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population, MUIR, A. D., *et al.* 373-377
- Measurement techniques, neuromuscular block,** Intraoperative assessment of atracurium-induced neuromuscular block using double burst stimulation, BRAUDE, N., *et al.* 574-578
- Measurement techniques, nuclear magnetic resonance,** Anaesthetic-plasma interactions: a study using nuclear magnetic resonance spectroscopy (MRS), EVANS, R. D., *et al.*, (ARS) 217P
- , Extradural haematoma after continuous extradural anaesthesia, TEKOK, I. H., *et al.* 112-115
- , Measurement of propofol metabolites in human urine using nuclear magnetic resonance, SNEYD, J. R., *et al.*, (ARS) 659-660P
- Measurement techniques, oximeters,** Computerized analysis of continuous pulse oximetry in children with nocturnal breathing disorders, WHEATLEY, R. G., *et al.*, (ARS) 208P
- , Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor, ANDREWS, P. J. D., *et al.* 553-558
- , Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704-711
- , Temperature dependence of LED and its theoretical effect on pulse oximetry, REYNOLDS, K. J., *et al.* 638-643
- Measurement techniques, plethysmography,** Rib cage contribution to resting and carbon dioxide stimulated ventilation during 1 MAC isoflurane anaesthesia, LUMB, A. B., *et al.* 712-721
- Measurement techniques, spectral analysis,** A new perspective on intraoperative monitoring of EEG, SNEYD, J. R., *et al.*, (ARS) 658P
- , Spectral analysis of the electromyogram: effect of fentanyl, SEVERN, A. M., *et al.*, (ARS) 650P
- Measurement techniques, thoracic impedance cardiography,** Non-invasive measurement of cardiac output by thoracic electrical bioimpedance: a study of reproducibility and comparison with thermodilution, JEWKES, C., *et al.* 788-794
- , Non-invasive measurement of cardiac output during induction of anaesthesia and tracheal intubation: thiopentone and propofol compared, VOHRA, A., *et al.* 64-68
- Measurement techniques, visual analogue scale,** Comparison of contemporaneous and retrospective assessment of postoperative pain using the visual analogue scale, LIU, W. H. D., *et al.* 768-771
- Medical Statistics on Microcomputers*, 1st Edn, BROWN, R. A., *et al.*, (R) 132-133

- Memory**, Changes in amplitude and latency of the P300 component of the auditory evoked potential with sedative and anaesthetic concentrations of nitrous oxide, JESSOP, J., *et al.* 524-531
- , Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam, PATTERSON, K. W., *et al.* 108-111
- Metabolism, endocrine**, Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic, CARLI, F., *et al.* 729-734
- Metabolism, energy expenditure**, Measurement of energy expenditure in critical illness using ^{13}C labelled bicarbonate, DEVLIN, J. C., *et al.* (ARS) 651P
- Metabolism, free radicals**, Direct evidence for free radical generation in experimental lung injury, MURPHY, P. G., *et al.* (ARS) 649-650P
- , The anti-oxidant potential of propofol, MURPHY, P. G., *et al.* (ARS) 209-210P
- Metabolism, lipid**, Anaesthetic-plasma interactions: a study using nuclear magnetic resonance spectroscopy (MRS), EVANS, R. D., *et al.* (ARS) 217P
- Metabolism, metabolites**, Measurement of propofol metabolites in human urine using nuclear magnetic resonance, SNEYD, J. R., *et al.* (ARS) 659-660P
- Metabolism, midazolam**, Midazolam and erythromycin, WOOD, M., (C) 131
- Metabolism, oxygen consumption**, Effect of inhaled salbutamol on resting oxygen consumption, AMOROSO, P., *et al.* (ARS) 210P
- , Resting energy expenditure in children with liver disease, WILSON, S. R., *et al.* (ARS) 216-217P
- Metabolism, protein**, Anaesthetic-plasma interactions: a study using nuclear magnetic resonance spectroscopy (MRS), EVANS, R. D., *et al.* (ARS) 217P
- , Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic, CARLI, F., *et al.* 729-734
- Metabolism, urinary conjugates**, Measurement of propofol metabolites in human urine using nuclear magnetic resonance, SNEYD, J. R., *et al.* (ARS) 659-660P
- Microcirculation**, Influence of hypertonic volume replacement on the microcirculation in cardiac surgery, BOLDT, J., *et al.* 595-602
- Model, lung**, First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model, PALAZZO, M. G. A., *et al.* 759-763
- Monitoring, apnoea**, AURA: a new respiratory monitor and apnoea alarm for spontaneously breathing patients, CYNA, A. M., *et al.* 341-345
- Monitoring, arterial pressure**, Comparison of invasive and non-invasive measurement of continuous arterial pressure using the Finapres, STOKES, D. N., *et al.* 26-35
- , Comparison of the Finapres and direct arterial pressure monitoring during profound hypotensive anaesthesia, AITKEN, H. A., *et al.* 36-40
- Monitoring, computerized**, A system for automatic feedback control of plasma potassium concentration, HEINING, M. P. D., *et al.* 120-126
- , Computerized analysis of continuous pulse oximetry in children with nocturnal breathing disorders, WHEATLEY, R. G., *et al.* (ARS) 208P
- Monitoring, depth of anaesthesia**, A new perspective on intraoperative monitoring of EEG, SNEYD, J. R., *et al.* (ARS) 658P
- , Systolic arterial pressure as a monitor of depth of anaesthesia, ASBURY, A. J., (C) 506
- , Systolic arterial pressure as a monitor of depth of anaesthesia, COUTO DA SILVA, J. M., (C) 506
- , Variations in respiratory sinus arrhythmia may reflect levels of anaesthesia, POMFRETT, C. J. D., *et al.* (ARS) 646-647P
- Monitoring, echocardiography**, Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities, DAVIES, K. R., *et al.* 58-63
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678-682
- , Haemodynamic effects of propofol: induction with 2.5 mg kg⁻¹, FAIRFIELD, J. E., *et al.* 618-620
- , Left ventricular function during transoesophageal echocardiographic assessment of abdominal aortic aneurysm resection, RYAN, T., *et al.* (ARS) 204-205P
- Monitoring, electrocardiography**, Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities, DAVIES, K. R., *et al.* 58-63
- , Postoperative myocardial ischaemia in patients with recent myocardial infarction, METZLER, H., *et al.* 317-319
- , Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population, MUIR, A. D., *et al.* 373-377
- Monitoring, electroencephalography**, A new perspective on intraoperative monitoring of EEG, SNEYD, J. R., *et al.* (ARS) 658P
- Monitoring, electro-oculogram**, Effect of 5% and 10% MAC of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.* (ARS) 212-213P
- , Effects of low concentrations of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.* 735-740
- Monitoring, evoked potentials**, Changes in amplitude and latency of the P300 component of the auditory evoked potential with sedative and anaesthetic concentrations of nitrous oxide, JESSOP, J., *et al.* 524-531
- , Does physiotherapy affect the auditory evoked potentials of sedated patients in the intensive care unit? SNEYD, J. R., *et al.* (ARS) 647P
- Monitoring, interstitial perfusion pressure**, Compartment syndrome after pressurized infusion, TOBIAS, M. D., *et al.* 332-334
- Monitoring, oxygen**, Computerized analysis of continuous pulse oximetry in children with nocturnal breathing disorders, WHEATLEY, R. G., *et al.* (ARS) 208P
- , Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor, ANDREWS, P. J. D., *et al.* 553-558
- , Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704-711
- , Response time of finger and ear pulse oximeter probes during hypoxaemic events occurring during anaesthesia, BROOME, I. J., *et al.* (ARS) 207P
- , Temperature dependence of LED and its theoretical effect on pulse oximetry, REYNOLDS, K. J., *et al.* 638-643
- , Video surveillance of oxygen administration by mask in postoperative patients, NOLAN, K. M., *et al.* (ARS) 650-651P
- Monitoring, respiratory sinus arrhythmia**, Variations in respiratory sinus arrhythmia may reflect levels of anaesthesia, POMFRETT, C. J. D., *et al.* (ARS) 646-647P
- Monitoring, ventilation**, AURA: a new respiratory monitor and apnoea alarm for spontaneously breathing patients, CYNA, A. M., *et al.* 341-345
- Mouse**, Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanum and strychnine, AL-MUHANDIS, W. M., *et al.* 608-613

- , Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice, STOTT, D. G., *et al.* 603–607
- Muscle skeletal, Jaw stiffness**—an ill understood condition, SADDLER, J. M., (*E*) 515–516
- Muscle skeletal, damage**, Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick, McLOUGHLIN, C., *et al.* 764–767
- Muscle skeletal, diaphragm**, Age-dependent variation in response to tubocurarine in the isolated rat diaphragm, MEAKIN, G., *et al.*, (*ARS*) 205–206P
- , Investigation of fade in suxamethonium-induced phase II block in the isolated rat diaphragm, GUPTA, V. L., *et al.*, (*ARS*) 211P
- Neonates**, Age-dependent variation in response to tubocurarine in the isolated rat diaphragm, MEAKIN, G., *et al.*, (*ARS*) 205–206P
- , Potency and ease of antagonism of pipecuronium in children, LEUWER, M., *et al.*, (*ARS*) 206–207P
- Nerve-muscle preparations**, Investigation of fade in suxamethonium-induced phase II block in the isolated rat diaphragm, GUPTA, V. L., *et al.*, (*ARS*) 211P
- Neuromuscular block, alcuronium**, Determinants of antagonism of non-depolarizing neuromuscular block, BREMER, G. H., *et al.*, (*C*) 362
- , Determinants of antagonism of non-depolarizing neuromuscular block, CAMPBELL, J. R., (*C*) 362
- Neuromuscular block, antagonism**, Antagonism of intense atracurium-induced neuromuscular block in children, GWINNUTT, C. L., *et al.* 13–16
- , Determinants of antagonism of non-depolarizing neuromuscular block, BREMER, G. H., *et al.*, (*C*) 362
- , Determinants of antagonism of non-depolarizing neuromuscular block, CAMPBELL, J. R., (*C*) 362
- , Dose requirements of neostigmine for antagonism of vecuronium neuromuscular block in the elderly: comparison with adults, MCCARTHY, G., *et al.*, (*ARS*) 652–653P
- , Potency and ease of antagonism of pipecuronium in children, LEUWER, M., *et al.*, (*ARS*) 206–207P
- , Potentiation and antagonism of vecuronium by decamethonium in man, FELDMAN, S. A., *et al.*, (*ARS*) 206P
- Neuromuscular block, atracurium**, Antagonism of intense atracurium-induced neuromuscular block in children, GWINNUTT, C. L., *et al.* 13–16
- , Atracurium and suxamethonium, DONATI, F., (*C*) 502
- , Atracurium and suxamethonium, FAUVEL, N. J., *et al.*, (*C*) 502
- , Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration, SHEARER, E. S., *et al.* 569–573
- , Determinants of antagonism of non-depolarizing neuromuscular block, BREMER, G. H., *et al.*, (*C*) 362
- , Determinants of antagonism of non-depolarizing neuromuscular block, CAMPBELL, J. R., (*C*) 362
- , Dose requirements of atracurium in paediatric intensive care patients, KUSHIMO, O. T., *et al.* 781–783
- , Intraoperative assessment of atracurium-induced neuromuscular block using double burst stimulation, BRAUDE, N., *et al.* 574–578
- , Pharmacokinetics of atracurium, BREMER, G. H., *et al.*, (*C*) 129–130
- , Pharmacokinetics of atracurium, PARKER, C. J. R., *et al.*, (*C*) 129
- , Resistance to atracurium in a patient with an increase in plasma alpha₁ globulins, TATMAN, A. J., *et al.* 623–625
- Neuromuscular block, dantrolene**, Serum concentrations of dantrolene following i.v. administration, LAURENCE, A. S., *et al.*, (*ARS*) 202–203P
- Neuromuscular block, decamethonium**, Potentiation and antagonism of vecuronium by decamethonium in man, FELDMAN, S. A., *et al.*, (*ARS*) 206P
- Neuromuscular block, laudanosine**, Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration, SHEARER, E. S., *et al.* 569–573
- , Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanosine and strychnine, AL-MUHANDIS, W. M., *et al.* 608–613
- Neuromuscular block, measurement of response**, Antagonism of intense atracurium-induced neuromuscular block in children, GWINNUTT, C. L., *et al.* 13–16
- , Intraoperative assessment of atracurium-induced neuromuscular block using double burst stimulation, BRAUDE, N., *et al.* 574–578
- Neuromuscular block, mivacurium**, Neuromuscular and clinical effects of mivacurium chloride in healthy adult patients during nitrous oxide–enflurane anaesthesia, GOLDHILL, D. R., *et al.* 289–295
- , Use of mivacurium chloride by constant infusion in the anephric patient, PHILLIPS, B. J., *et al.*, (*ARS*) 653–654P
- Neuromuscular block, pipecuronium**, Comparative effects of pipecuronium and tubocurarine on plasma concentrations of histamine in humans, NAGUIB, M., *et al.* 320–322
- , Potency and ease of antagonism of pipecuronium in children, LEUWER, M., *et al.*, (*ARS*) 206–207P
- Neuromuscular block, potentiation**, Potentiation and antagonism of vecuronium by decamethonium in man, FELDMAN, S. A., *et al.*, (*ARS*) 206P
- Neuromuscular block, recovery**, Investigation of fade in suxamethonium-induced phase II block in the isolated rat diaphragm, GUPTA, V. L., *et al.*, (*ARS*) 211P
- , Neuromuscular and clinical effects of mivacurium chloride in healthy adult patients during nitrous oxide–enflurane anaesthesia, GOLDHILL, D. R., *et al.* 289–295
- , Post-Post-Tetanic Facilitation Fade (PPTFF), BLACK, A. M. S., *et al.*, (*ARS*) 220P
- Neuromuscular block, resistance**, Resistance to atracurium in a patient with an increase in plasma alpha₁ globulins, TATMAN, A. J., *et al.* 623–625
- , Resistance to non-depolarizing neuromuscular blocking agents, HUNTER, J. M., (*E*) 511–514
- Neuromuscular block, suxamethonium**, Atracurium and suxamethonium, DONATI, F., (*C*) 502
- , Atracurium and suxamethonium, FAUVEL, N. J., *et al.*, (*C*) 502
- , Interference with pacemaker function, FINFER, S. R., (*C*) 664–665
- , Interference with pacemaker function, SIDHU, V. S., (*C*) 664
- , Investigation of fade in suxamethonium-induced phase II block in the isolated rat diaphragm, GUPTA, V. L., *et al.*, (*ARS*) 211P
- , Morbidity following day-case procedures, SMITH, S. O., *et al.*, (*ARS*) 644–645P
- , Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick, McLOUGHLIN, C., *et al.* 764–767
- , Serum concentrations of dantrolene following i.v. administration, LAURENCE, A. S., *et al.*, (*ARS*) 202–203P
- Neuromuscular block, tubocurarine**, Age-dependent variation in response to tubocurarine in the isolated rat diaphragm, MEAKIN, G., *et al.*, (*ARS*) 205–206P
- , Comparative effects of pipecuronium and tubocurarine on plasma concentrations of histamine in humans, NAGUIB, M., *et al.* 320–322
- , Investigation of fade in suxamethonium-induced

- phase II block in the isolated rat diaphragm, GUPTA, V. L., *et al.*, (ARS) 211P
- Neuromuscular block, vecuronium**, Dose requirements of neostigmine for antagonism of vecuronium neuromuscular block in the elderly: comparison with adults, MCCARTHY, G., *et al.*, (ARS) 652-653P
- , Interaction between betamethasone and vecuronium, PARR, S. M., *et al.* 447-451
- , Potentiation and antagonism of vecuronium by decamethonium in man, FELDMAN, S. A., *et al.*, (ARS) 206P
- Operating rooms, contamination**, Determination of contamination of a chemical warfare-proof operating theatre with volatile anaesthetic agents and assessment of anaesthetic gas scavenging systems, YOGANATHAN, S., *et al.* 614-617
- Operating rooms, exhaust systems**, Determination of contamination of a chemical warfare-proof operating theatre with volatile anaesthetic agents and assessment of anaesthetic gas scavenging systems, YOGANATHAN, S., *et al.* 614-617
- Oxygen, consumption**, Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia, DELAUNAY, L., *et al.* 397-401
- Oxygen, delivery systems**, Non-cardiogenic pulmonary oedema after transfusion with granulocyte antibody containing blood: treatment with extracorporeal membrane oxygenation, WORSLEY, M. H., *et al.* 116-119
- , Preoxygenation: use of a high flow delivery system, OOI, R., *et al.*, (ARS) 208P
- , The pneuPAC hyperbaric variant HB: a ventilator suitable for use within a one-man hyperbaric chamber, SPITAL, M. J., *et al.* 488-491
- , Video surveillance of oxygen administration by mask in postoperative patients, NOLAN, K. M., *et al.*, (ARS) 650-651P
- Oxygen, saturation**, Desaturation and induction characteristics: comparison of propofol and thiopentone during mask anaesthesia with isoflurane, HEAD-RAPSON, A. G., *et al.*, (ARS) 203P
- , Desaturation during total knee replacement, AL-SHAIKH, B., (C) 502
- , Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen, REEDER, M. K., *et al.* 326-328
- , Nitrous oxide sedation causes post-hyperventilation apnoea, NORTHWOOD, D., *et al.* 7-12
- , Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704-711
- Oxygen, therapy**, AURA: a new respiratory monitor and apnoea alarm for spontaneously breathing patients, CYNA, A. M., *et al.* 341-345
- , Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen, REEDER, M. K., *et al.* 326-328
- , The pneuPAC hyperbaric variant HB: a ventilator suitable for use within a one-man hyperbaric chamber, SPITAL, M. J., *et al.* 488-491
- Oxygen, transport**, Haemodynamic and oxygen transport effects of isoflurane as sedation in ventilated patients in the intensive care unit, BROWNE, G. P. R., *et al.*, (ARS) 652P
- Pain, acute**, The first year's experience of an acute pain service, WHEATLEY, R. G., *et al.* 353-359
- Pain, injection**, Pain on injection of propofol: effects of concentration and diluent, KLEMENT, W., *et al.* 281-284
- , Pain on i.v. injection, KHUENL-BRADY, K. S., *et al.*, (C) 506-507
- , Pain on i.v. injection, KLEMENT, W., *et al.*, (C) 507
- Pain, postoperative**, Comparison of contemporaneous and retrospective assessment of postoperative pain using the visual analogue scale, LIU, W. H. D., *et al.* 768-771
- , Pain after surgery, SMITH, G., (E) 233-234
- , The first year's experience of an acute pain service, WHEATLEY, R. G., *et al.* 353-359
- Partial pressure, carbon dioxide**, Effect of P_{aCO_2} on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat, YOUNG, W. L., *et al.* 440-446
- Pharmacokinetics, alfentanil**, Pharmacokinetics of alfentanil in burns patients, MACFIE, A. G., *et al.*, (ARS) 657P
- Pharmacokinetics, atracurium**, Atracurium and suxamethonium, DONATI, F., (C) 502
- , Atracurium and suxamethonium, FAUVEL, N. J., *et al.*, (C) 502
- , Pharmacokinetics of atracurium, BEEMER, G. H., *et al.*, (C) 129-130
- , Pharmacokinetics of atracurium, PARKER, C. J. R., *et al.*, (C) 129
- Pharmacokinetics, bupivacaine**, Cardiovascular effects and regional clearances of i.v. bupivacaine in sheep: enantiomeric analysis, RUTTEN, A. J., *et al.* 247-256
- , Disposition of mepivacaine and bupivacaine enantiomers in sheep, MATHER, L. E. 239-246
- , Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block, PIHLAJAMÄKI, K. K. 621-622
- Pharmacokinetics, cisapride**, Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine, ROWBOTHAM, D. J., *et al.* 302-305
- Pharmacokinetics, ketamine**, Pharmacokinetics and distribution of ketamine after extradural administration to dogs, PEDRAZ, J. L., *et al.* 310-316
- Pharmacokinetics, mepivacaine**, Disposition of mepivacaine and bupivacaine enantiomers in sheep, MATHER, L. E. 239-246
- Pharmacokinetics, mivacurium**, Use of mivacurium chloride by constant infusion in the anephric patient, PHILLIPS, B. J., *et al.*, (ARS) 653-654P
- Pharmacokinetics, models**, Pharmacokinetic model driven infusion of propofol in children, MARSH, B., *et al.* 41-48
- Pharmacokinetics, morphine**, Effect of cisapride on morphine absorption after oral administration of sustained-release morphine, ROWBOTHAM, D. J., *et al.* 421-425
- , Physiological disposition of i.v. morphine in sheep, SLOAN, P. A., *et al.* 378-386
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, DAVIS, C. L., (C) 362-363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, HANNA, M. H., (C) 363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, JOEL, P., (C) 363
- Pharmacokinetics, morphine-6-glucuronide**, Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, DAVIS, C. L., (C) 362-363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, HANNA, M. H., (C) 363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, JOEL, P., (C) 363
- Pharmacokinetics, propofol**, Disposition of propofol at Caesarean section and in the postpartum period, GIN, T., *et al.* 49-53
- Pharmacokinetics, ranitidine**, Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine, ROWBOTHAM, D. J., *et al.* 302-305
- Pharmacokinetics, stereoisomers**, Cardiovascular effects

- and regional clearances of i.v. bupivacaine in sheep: enantiomeric analysis, RUTTEN, A. J., *et al.* 247-256
- , Disposition of mepivacaine and bupivacaine enantiomers in sheep, MATHER, L. E. 239-246
- Pharmacokinetics, uptake**, Change in end-expiratory respiratory volume with thiopentone or propofol induction of anaesthesia, RUTHERFORD, J. S., *et al.*, (ARS) 647P
- , First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model, PALAZZO, M. G. A., *et al.* 759-763
- , Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block, PIHLAJAMÄKI, K. K. 621-622
- , Total i.v. anaesthesia with propofol and alfentanil: influence of age and weight on dose requirements, RAFTERY, S., *et al.*, (ARS) 218P
- Pharmacology, betamethasone**, Interaction between betamethasone and vecuronium, PARR, S. M., *et al.* 447-451
- Pharmacology, clonidine**, Preanaesthetic medication with clonidine: a dose-response study, CARABINE, U. A., *et al.* 79-83
- Pharmacology, diamorphine**, Speed of onset of analgesia of diamorphine or morphine, SHELLY, M. P., *et al.*, (C) 666
- Pharmacology, dobutamine**, Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine, WENSTONE, R., *et al.* 591-594
- Pharmacology, dopamine**, Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine, WENSTONE, R., *et al.* 591-594
- Pharmacology, dose-response**, Age-dependent variation in response to tubocurarine in the isolated rat diaphragm, MEAKIN, G., *et al.*, (ARS) 205-206P
- , Dose requirements of neostigmine for antagonism of vecuronium neuromuscular block in the elderly: comparison with adults, MCCARTHY, G., *et al.*, (ARS) 652-653P
- , Dose requirements to suppress consciousness by continuous infusion of propofol in young adults, DUNNET, J. M., *et al.*, (ARS) 214-215P
- , Preanaesthetic medication with clonidine: a dose-response study, CARABINE, U. A., *et al.* 79-83
- , Propofol and midazolam act synergistically in combination, SHORT, T. G., *et al.* 539-545
- , Thiopentone-propofol hypnotic synergism in patients, NAGUIB, M., *et al.* 4-6
- Pharmacology, milrinone**, Clinical and haemodynamic effects of milrinone in the treatment of low cardiac output after cardiac surgery, WRIGHT, E. M., *et al.* 585-590
- Pharmacology, mivacurium**, Neuromuscular and clinical effects of mivacurium chloride in healthy adult patients during nitrous oxide-enflurane anaesthesia, GOLDHILL, D. R., *et al.* 289-295
- Pharmacology, morphine**, Speed of onset of analgesia of diamorphine or morphine, SHELLY, M. P., *et al.*, (C) 666
- Pharmacology, Picolax**, Picolax bowel preparation, DODSON, M. E., (C) 664
- Pharmacology, salbutamol**, Effect of inhaled salbutamol on resting oxygen consumption, AMOROSO, P., *et al.*, (ARS) 210P
- Pharmacology, synergism**, Potentiation and antagonism of vecuronium by decamethonium in man, FELDMAN, S. A., *et al.*, (ARS) 206P
- , Propofol and midazolam act synergistically in combination, SHORT, T. G., *et al.* 539-545
- , Synergism among i.v. anaesthetics, MCKAY, A. C., (E) 1-3
- , Thiopentone-propofol hypnotic synergism in patients, NAGUIB, M., *et al.* 4-6
- Physiotherapy**, Does physiotherapy affect the auditory evoked potentials of sedated patients in the intensive care unit? SNEYD, J. R., *et al.*, (ARS) 647P
- Placenta, blood flow**, Assessment of the placental circulation, MOORE, J., (E) 671-673
- , Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the feto-placental unit during elective Caesarean section, McLINTIC, A. J., *et al.* 683-689
- , Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms, TURNER, G. A., *et al.* 306-309
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678-682
- Position, effects**, Effect of supine and lateral positions on airway patency in anaesthetized patients, SWANN, D. G., *et al.*, (ARS) 644P
- Position, prone**, The prone position for the surgical patient: a historical review of the principles and hazards, ANDERTON, J. M. 452-463
- Position, sitting**, Tracheal intubation with the patient in a sitting position, BROCK-UTNE, J. G., *et al.*, (C) 225-226
- , Tracheal intubation with the patient in the sitting position, ADAMS, A. K., (C) 804
- Postanaesthetic Care*, FROST, E. A. M., *et al.*, (editors), (R) 133
- Potency, anaesthetic, age factors**, Total i.v. anaesthesia with propofol and alfentanil: influence of age and weight on dose requirements, RAFTERY, S., *et al.*, (ARS) 218P
- Potency, anaesthetic, ED₅₀**, Dose requirements to suppress consciousness by continuous infusion of propofol in young adults, DUNNET, J. M., *et al.*, (ARS) 214-215P
- , Thiopentone-propofol hypnotic synergism in patients, NAGUIB, M., *et al.* 4-6
- Potency, drug**, Potency and ease of antagonism of pipecuronium in children, LEUWER, M., *et al.*, (ARS) 206-207P
- Potency, drug, age factors**, Dose requirements of atracurium in paediatric intensive care patients, KUSHIMO, O. T., *et al.* 781-783
- Potency, drug, tolerance**, Dose requirements of atracurium in paediatric intensive care patients, KUSHIMO, O. T., *et al.* 781-783
- , Resistance to atracurium in a patient with an increase in plasma alpha₁ globulins, TATMAN, A. J., *et al.* 623-625
- , Resistance to non-depolarizing neuromuscular blocking agents, HUNTER, J. M., (E) 511-514
- Pregnancy**, Disposition of propofol at Caesarean section and in the postpartum period, GIN, T., *et al.* 49-53
- , Gastric emptying in pregnancy, MACFIE, A. G., *et al.* 54-57
- , Management of labour and delivery in patients with intracranial neoplasms, FINFER, S. R. 784-787
- Premedication, clonidine**, Preanaesthetic medication: comparison of three drug groups, CARABINE, U. A., *et al.*, (ARS) 659P
- , Preanaesthetic medication with clonidine: a dose-response study, CARABINE, U. A., *et al.* 79-83
- Premedication, dexmedetomidine**, A comparison of dexmedetomidine, an alpha₂-adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery, AANTAA, R., *et al.* 402-409
- Premedication, diazepam**, Investigation of the effect of

- oral diazepam on upper airway reactivity, MURPHY, P. J., *et al.*, (ARS) 660-661P
- Premedication, glycopyrronium**, Can glycopyrronium attenuate propofol-induced hypotension in elderly patients? SNEYD, J. R., *et al.*, (ARS) 661-662P
- Premedication, midazolam**, A comparison of dexmedetomidine, an α_2 -adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery, AANTAA, R., *et al.* 402-409
- Premedication, temazepam**, Preanaesthetic medication: comparison of three drug groups, CARABINE, U. A., *et al.*, (ARS) 659P
- , Preanaesthetic medication with clonidine: a dose-response study, CARABINE, U. A., *et al.* 79-83
- Premedication, timolol**, Preanaesthetic medication: comparison of three drug groups, CARABINE, U. A., *et al.*, (ARS) 659P
- Protein, binding**, Resistance to atracurium in a patient with an increase in plasma α_1 globulins, TATMAN, A. J., *et al.* 623-625
- Protein, globulin**, Resistance to atracurium in a patient with an increase in plasma α_1 globulins, TATMAN, A. J., *et al.* 623-625
- Protein, metabolism**, Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic, CARLI, F., *et al.* 729-734
- Protein, plasma**, Anaesthetic-plasma interactions: a study using nuclear magnetic resonance spectroscopy (MRS), EVANS, R. D., *et al.*, (ARS) 217P
- Psychological responses**, Effects of i.v. lignocaine on psychological performance and subjective state in healthy volunteers, ARMSTRONG, P. J., *et al.* 532-538
- Psychological responses, postoperative**, Mental function after general anaesthesia for transurethral procedures, SMITH, C., *et al.* 262-268
- Rabbit**, Anaesthetic-plasma interactions: a study using nuclear magnetic resonance spectroscopy (MRS), EVANS, R. D., *et al.*, (ARS) 217P
- , First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model, PALAZZO, M. G. A., *et al.* 759-763
- , Intra-arterial thiopentone is directly toxic to vascular endothelium, MACPHERSON, R. D., *et al.* 546-552
- , Pressure-volume hysteresis of the lungs in respiratory distress syndrome, RATCLIFFE, F. M., *et al.*, (ARS) 203-204P
- Rat**, Age-dependent variation in response to tubocurarine in the isolated rat diaphragm, MEAKIN, G., *et al.*, (ARS) 205-206P
- , Effect of P_{aCO_2} on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat, YOUNG, W. L., *et al.* 440-446
- , Interaction between betamethasone and vecuronium, PARR, S. M., *et al.* 447-451
- Receptors, opioid**, Opioid receptors—the role of the sigma receptor? CHURCH, J., (C) 361-362
- , Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice, STOTT, D. G., *et al.* 603-607
- Records, anaesthesia**, Reporting of deaths, LUNN, J., (C) 503
- Recovery**, Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia, DELAUNAY, L., *et al.* 397-401
- , Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia, NAITO, Y., *et al.* 387-389
- Recovery, postoperative**, Influence of therapeutic suggestions during general anaesthesia on recovery in patients undergoing hysterectomy, LIU, D. W. H., *et al.*, (ARS) 208-209P
- Recovery, psychomotor**, Alcohol after sedation with i.v. midazolam-fentanyl: effects on psychomotor functioning, LICHTOR, J. L., *et al.* 579-584
- , Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam, PATTERSON, K. W., *et al.* 108-111
- Reflexes, laryngeal**, A portable method to assess upper airway reactivity, LANGTON, J., *et al.*, (ARS) 648-649P
- , Investigation of the effect of oral diazepam on upper airway reactivity, MURPHY, P. J., *et al.*, (ARS) 660-661P
- Regional Anaesthesia**, 2nd Edn, KOERSTER, W., *et al.*, (editors), (R) 668
- Regional Anaesthesia in Children**, 1st Edn, SAINT-MAURICE, C., *et al.*, (editors), (R) 132
- Safety, drug**, Bacterial growth in propofol, MCLEOD, G. A., *et al.*, (C) 665-666
- Screening**, Screening for antibodies associated with halothane hepatitis, HASTINGS, K. L., *et al.* 722-728
- Sedation**, Antagonism of benzodiazepine sedation with flumazenil, McCLOY, R., *et al.*, (C) 504
- , Antagonism of benzodiazepine sedation with flumazenil, SANDERS, L., *et al.*, (C) 504
- , Diprivan intensive care sedation in children, RODGERS, E. M., (C) 505
- , Does physiotherapy affect the auditory evoked potentials of sedated patients in the intensive care unit? SNEYD, J. R., *et al.*, (ARS) 647P
- , Effects of low concentrations of cyclopropane and halothane on peak velocity of saccadic eye movements, YOSHIZUMI, J., *et al.* 735-740
- , Haemodynamic and oxygen transport effects of isoflurane as sedation in ventilated patients in the intensive care unit, BROWNE, G. P. R., *et al.*, (ARS) 652P
- , Nitrous oxide sedation causes post-hyperventilation apnoea, NORTHWOOD, D., *et al.* 7-12
- , Patient-controlled anxiety with propofol, URE, R. W., *et al.*, (ARS) 657-658P
- , Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam, PATTERSON, K. W., *et al.* 108-111
- , Sedation with propofol during surgery under regional block: evaluation of a computer controlled infusion system, SKIPSEY, I. G., *et al.*, (ARS) 218-219P
- Sheep**, Cardiovascular effects and regional clearances of i.v. bupivacaine in sheep: enantiomeric analysis, RUTTEN, A. J., *et al.* 247-256
- , Disposition of mepivacaine and bupivacaine enantiomers in sheep, MATHER, L. E. 239-246
- , Femoral arteriovenous extracorporeal removal of carbon dioxide using a hollow fibre membrane lung, YOUNG, J. D., *et al.*, (ARS) 209P
- , Physiological disposition of i.v. morphine in sheep, SLOAN, P. A., *et al.* 378-386
- Sleep apnoea**, Computerized analysis of continuous pulse oximetry in children with nocturnal breathing disorders, WHEATLEY, R. G., *et al.*, (ARS) 208P
- , Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen, REEDER, M. K., *et al.* 326-328
- Spinal cord, sensory block**, Spinally mediated antinociceptive effects of xylazine, an α_2 -adrenoceptor agonist: interaction with spinal cord opioid pathways, GOODCHILD, C. S., *et al.*, (ARS) 201P
- Spinal cord, vertebral interspace**, Regional anaesthesia requires attention to detail, LEVINS, F. A., (C) 225
- , Regional anaesthesia requires attention to detail, WILDSMITH, J. A. W., (C) 224-225
- Stress**, Comparison of sufentanil-nitrous oxide anaesthesia

- with fentanyl-nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery, KIEZMANN, D., *et al.* 269-276
- , Effects of labetalol on perioperative stress markers and isoflurane requirements, AMAR, D., *et al.* 296-301
- , Relationship between exercise-induced myolysis and malignant hyperthermia, HACKL, W., *et al.*, (C) 221
- , Relationship between exercise-induced myolysis and malignant hyperthermia, KRIVOSIC-HORBER, R., *et al.*, (C) 221
- Stress, metabolic response**, Metabolic response to colonic surgery: extradural *vs* continuous spinal, WEBSTER, J., *et al.* 467-469
- Surgery, Potassium in the perioperative period**, VAUGHAN, R. S. 194-200
- Surgery, abdominal**, Comparison of sufentanil-nitrous oxide anaesthesia with fentanyl-nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery, KIEZMANN, D., *et al.* 269-276
- , Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac, BURNS, J. W., *et al.* 235-238
- , Ketamine for caudal analgesia in children: comparison with caudal bupivacaine, NAGUIB, M., *et al.* 559-564
- , Midazolam modifies pancreatic and anterior pituitary hormone secretion during upper abdominal surgery, DESBOROUGH, J. P., *et al.* 390-396
- , Pain relief and hypoxaemia during administration of extradural fentanyl by three different methods, KLUGER, M. T., *et al.*, (ARS) 656-657P
- , Picolax bowel preparation, DODSON, M. E., (C) 664
- , Postoperative analgesia by infusion of local anaesthetic into the rectus sheath, WATSON, D., *et al.*, (ARS) 656P
- , Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic, CARLI, F., *et al.* 729-734
- , Resistance to atracurium in a patient with an increase in plasma alpha₁ globulins, TATMAN, A. J., *et al.* 623-625
- Surgery, aneurysm**, Controlled hypotension for cerebral aneurysm surgery in the presence of severe aortic coarctation, GOODIE, D. B., *et al.* 329-331
- Surgery, brain**, Controlled hypotension for cerebral aneurysm surgery in the presence of severe aortic coarctation, GOODIE, D. B., *et al.* 329-331
- , Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy, KNUDSEN, L., *et al.* 277-280
- Surgery, cardiovascular**, Clinical and haemodynamic effects of milrinone in the treatment of low cardiac output after cardiac surgery, WRIGHT, E. M., *et al.* 585-590
- , Cuffed tracheal tubes for paediatric cardiac surgery cause a low incidence of postoperative airway problems, MALMROS, C., *et al.*, (ARS) 655P
- , Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass, BOER, F., *et al.* 69-72
- , Enoximone during coronary bypass surgery, RAFTERY, S., *et al.*, (ARS) 651-652P
- , Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen, REEDER, M. K., *et al.* 326-328
- , Influence of hypertonic volume replacement on the microcirculation in cardiac surgery, BOLDT, J., *et al.* 595-602
- , Left ventricular function during transoesophageal echocardiographic assessment of abdominal aortic aneurysm resection, RYAN, T., *et al.*, (ARS) 204-205P
- , Non-cardiogenic pulmonary oedema after transfusion with granulocyte antibody containing blood: treatment with extracorporeal membrane oxygenation, WORSLEY, M. H., *et al.* 116-119
- , Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia, REEDER, M. K., *et al.* 626-631
- , Relationship between perioperative ischaemic and hypoxic events in patients with cardiovascular disease, GILL, N., *et al.*, (ARS) 649P
- , Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine, WENSTONE, R., *et al.* 591-594
- Surgery, colon**, Metabolic response to colonic surgery: extradural *vs* continuous spinal, WEBSTER, J., *et al.* 467-469
- Surgery, day-case**, Patient-controlled anxiolysis with propofol, URE, R. W., *et al.*, (ARS) 657-658P
- , Serum concentrations of dantrolene following i.v. administration, LAURENCE, A. S., *et al.*, (ARS) 202-203P
- Surgery, gynaecological**, A comparison of dexmedetomidine, an alpha₂-adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery, AANTAA, R., *et al.* 402-409
- , Influence of therapeutic suggestions during general anaesthesia on recovery in patients undergoing hysterectomy, LIU, D. W. H., *et al.*, (ARS) 208-209P
- , Morbidity following day-case procedures, SMITH, S. O., *et al.*, (ARS) 644-645P
- Surgery, non-cardiac**, Postoperative myocardial ischaemia in patients with recent myocardial infarction, METZLER, H., *et al.* 317-319
- Surgery, ophthalmological**, Comparison of laryngeal mask airway with tracheal intubation for intraocular surgery, AKHTAR, T. M., *et al.*, (ARS) 215P
- , Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction, LEWIS, I. H., *et al.* 73-78
- Surgery, oral**, Serum concentrations of dantrolene following i.v. administration, LAURENCE, A. S., *et al.*, (ARS) 202-203P
- Surgery, orthopaedic**, Desaturation during total knee replacement, AL-SHAIKH, B., (C) 502
- , Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients, SHARROCK, N. E., *et al.* 694-698
- , Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty, SHARROCK, N. E., *et al.* 17-25
- , Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block, PIHLAJAMÄKI, K. K. 621-622
- Surgery, otolaryngological**, P6 acupuncture and postoperative vomiting after tonsillectomy in children, YENTIS, S. M., *et al.* 779-780
- Surgery, paediatric**, Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine, WENSTONE, R., *et al.* 591-594
- Surgery, post-transplantation**, Anaesthesia for patients with transplanted hearts and lungs undergoing non-cardiac surgery, SHAW, I. H., *et al.* 772-778
- Surgery, preoperative period**, Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population, MUIR, A. D., *et al.* 373-377
- , Silent myocardial ischaemia in preoperative patients:

- what does it mean, and what should be done about it? DE BONO, D. P., *et al.*, (E) 367-368
- Surgery, spinal**, The prone position for the surgical patient: a historical review of the principles and hazards, ANDERTON, J. M. 452-463
- Surgery, thoracic**, Patterns of oxygenation after thoracotomy, ENTWISTLE, M. D., *et al.* 704-711
- Surgery, urological**, Dilutional hyponatraemia following transurethral operation for clot retention, HAHN, R. G. 339-340
- , Mental function after general anaesthesia for transurethral procedures, SMITH, C., *et al.* 262-268
- Surgery, vascular**, Repair of traumatic transection of the thoracic aorta: esmolol for intraoperative control of arterial pressure, FENNER, S. G., *et al.* 483-487
- Sympathetic nervous system, adrenaline**, Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients, SHARROCK, N. E., *et al.* 694-698
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678-682
- Sympathetic nervous system, adrenergic block**, Spinally mediated antinociceptive effects of xylazine, an alpha-2 adrenoceptor agonist: interaction with spinal cord opioid pathways, GOODCHILD, C. S., *et al.*, (ARS) 201P
- Sympathetic nervous system, clonidine**, Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia, DELAUNAY, L., *et al.* 397-401
- , Preanaesthetic medication with clonidine: a dose-response study, CARABINE, U. A., *et al.* 79-83
- , Spinally mediated antinociceptive effects of xylazine, an alpha-2 adrenoceptor agonist: interaction with spinal cord opioid pathways, GOODCHILD, C. S., *et al.*, (ARS) 201P
- Sympathetic nervous system, labetalol**, Effects of labetalol on perioperative stress markers and isoflurane requirements, AMAR, D., *et al.* 296-301
- Sympathetic nervous system, magnesium sulphate**, Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section, ASHTON, W. B., *et al.* 741-747
- Sympathetic nervous system, phenylephrine**, Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients, SHARROCK, N. E., *et al.* 694-698
- Sympathetic nervous system, pindolol**, Effects of pindolol on the cardiovascular response to tracheal intubation, MIKAWA, K., *et al.* 416-420
- Sympathetic nervous system, sympathoadrenal responses**, A comparison of dexmedetomidine, an alpha₂-adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery, AANTAA, R., *et al.* 402-409
- , Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section, ASHTON, W. B., *et al.* 741-747
- , Comparison of sufentanil-nitrous oxide anaesthesia with fentanyl-nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery, KIETZMANN, D., *et al.* 269-276
- , Effects of labetalol on perioperative stress markers and isoflurane requirements, AMAR, D., *et al.* 296-301
- Sympathetic nervous system, xylazine**, Spinally mediated antinociceptive effects of xylazine, an alpha-2 adrenoceptor agonist: interaction with spinal cord opioid pathways, GOODCHILD, C. S., *et al.*, (ARS) 201P
- Temperature, regulation**, Maternal temperature regulation during extradural analgesia for labour, CAMANN, W. R., *et al.* 565-568
- The Anaesthetic Plan: From Physiologic Principles to Clinical Strategies**, MURAVCHICK, S., (R) 365
- The Lung—Scientific Foundations**, CRYSTAL, R. G., *et al.*, (editors), (R) 230
- Towards a New Pharmacotherapy of Pain**, BASBAUM, A. I., *et al.*, (editors), (R) 805
- Toxicity, Anaesthesia and bone marrow aplasia**, FENNER, S. G., *et al.*, (C) 665
- , Anaesthesia and bone marrow aplasia, HAMILTON, W. K., (C) 665
- , Intra-arterial thiopentone is directly toxic to vascular endothelium, MACPHERSON, R. D., *et al.* 546-552
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, DAVIS, C. L., (C) 362-363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, HANNA, M. H., (C) 363
- , Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide, JOEL, P., (C) 363
- Transfusion, autotransfusion**, Inappropriate heparinization with a cell saver, COLUMB, M. O., (C) 223
- Transfusion, complications**, Inappropriate heparinization with a cell saver, COLUMB, M. O., (C) 223
- Transfusion, stored blood**, Non-cardiogenic pulmonary oedema after transfusion with granulocyte antibody containing blood: treatment with extracorporeal membrane oxygenation, WORSLEY, M. H., *et al.* 116-119
- Trauma Anaesthesia**, STERNE, J. K., *et al.*, (editors), (R) 508
- Uterus, adrenaline**, Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the feto-placental unit during elective Caesarean section, McLINTIC, A. J., *et al.* 683-689
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678-682
- Uterus, blood flow**, Assessment of the placental circulation, MOORE, J., (E) 671-673
- , Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the feto-placental unit during elective Caesarean section, McLINTIC, A. J., *et al.* 683-689
- , Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation, ALAHUHTA, S., *et al.* 678-682
- Veins, complications**, Deep venous thrombosis and anaesthesia, JØRGENSEN, L. N., (C) 128
- , Deep venous thrombosis and anaesthesia, MCKENZIE, P. J., (C) 128
- , Deep venous thrombosis and anaesthesia, MODIG, J., (C) 127-128
- , Deep venous thrombosis and anaesthesia, MODIG, J., (C) 128
- , Superior sagittal sinus thrombosis after internal jugular vein cannulation, STEPHENS, P. H., *et al.* 476-479
- , Venous sequelae after i.v. diclofenac, CAMPBELL, W., *et al.*, (C) 803
- , Venous sequelae after i.v. diclofenac, GOPINATH, R., (C) 803
- Veins, jugular, cannulation**, Jugular bulb cannulation: description of a cannulation technique and validation of

- a new continuous monitor, ANDREWS, P. J. D., *et al.* 553-558
- , Superior sagittal sinus thrombosis after internal jugular vein cannulation, STEPHENS, P. H., *et al.* 476-479
- Veins, subclavian, cannulation**, Delayed pneumothorax after subclavian vein catheterization and positive pressure ventilation, CRONEN, M. C., *et al.* 480-482
- Veins, vasodilatation**, Propofol induces the production of endothelium-derived relaxing factor, PETROS, A. J., *et al.*, (ARS) 645-646P
- Ventilation, eucapnic response**, Hyperventilation and blood concentrations of propofol during total i.v. anaesthesia, ENEVER, G., *et al.*, (ARS) 217-218P
- Ventilation, high frequency**, Pressure-volume hysteresis of the lungs in respiratory distress syndrome, RATCLIFFE, F. M., *et al.*, (ARS) 203-204P
- Ventilation, high frequency jet**, Pressure support ventilation using a new tracheal gas injection tube, BEYDON, L., *et al.* 795-800
- Ventilation, hyperventilation**, Hyperventilation and blood concentrations of propofol during total i.v. anaesthesia, ENEVER, G., *et al.*, (ARS) 217-218P
- , Nitrous oxide sedation causes post-hyperventilation apnoea, NORTHWOOD, D., *et al.* 7-12
- Ventilation, hypocapnic response**, Hyperventilation and blood concentrations of propofol during total i.v. anaesthesia, ENEVER, G., *et al.*, (ARS) 217-218P
- Ventilation, mechanical**, Dose requirements of atracurium in paediatric intensive care patients, KUSHIMO, O. T., *et al.* 781-783
- , Tension pneumothorax—wrong tube? KNEESHAW, J. D., (C) 222-223
- Ventilation, obstruction**, Computerized analysis of continuous pulse oximetry in children with nocturnal breathing disorders, WHEATLEY, R. G., *et al.*, (ARS) 208P
- Ventilation, pattern**, Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen, REEDER, M. K., *et al.* 326-328
- , Nitrous oxide sedation causes post-hyperventilation apnoea, NORTHWOOD, D., *et al.* 7-12
- Ventilation, pressure support**, Pressure support ventilation using a new tracheal gas injection tube, BEYDON, L., *et al.* 795-800
- Ventilation, rib cage**, A rapid method to assess chest wall shape and volume change, DRUMMOND, G. B., *et al.*, (ARS) 204P
- , Rib cage contribution to resting and carbon dioxide stimulated ventilation during 1 MAC isoflurane anaesthesia, LUMB, A. B., *et al.* 712-721
- Vomiting, antiemetics**, Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction, LEWIS, I. H., *et al.* 73-78
- , Use of buccal prochlorperazine in the prevention of postoperative sickness, PATTERSON, K. W., *et al.*, (ARS) 213-214P
- Vomiting, incidence**, Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction, LEWIS, I. H., *et al.*, 73-78
- , Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass, BOER, F., *et al.* 69-72
- , P6 acupuncture and postoperative vomiting after tonsillectomy in children, YENTIS, S. M., *et al.* 779-780
- , Relationship of postoperative and cancer chemotherapy sickness, DUNDEE, J. W., *et al.*, (ARS) 214P
- Vomiting, nausea**, Relationship of postoperative and cancer chemotherapy sickness, DUNDEE, J. W., *et al.*, (ARS) 214P

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JULY

- EDITORIAL: Synergism among i.v. anaesthetics ...
A. C. McKay

ORIGINAL ARTICLES

- Thiopentone-propofol hypnotic synergism in patients
M. Naguib and A. Sari-Kouzel

- Nitrous oxide sedation causes post-hyperventilation apnoea
D. Northwood, D. J. Sapsford, J. G. Jones, D. Griffiths and C. Wilkins

- Antagonism of intense atracurium-induced neuromuscular block in children
C. L. Gwinnett, R. W. M. Walker and G. Meakin

- Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty
N. E. Sharrock, R. Mineo and B. Urquhart

- Comparison of invasive and non-invasive measurement of continuous arterial pressure using the Finapres
D. N. Stokes, T. Clutton-Brock, C. Patil, J. M. Thompson and P. Hutton

- Comparison of the Finapres and direct arterial pressure monitoring during profound hypotensive anaesthesia
H. A. Aitken, J. G. Todd and G. N. C. Kenny

- Pharmacokinetic model driven infusion of propofol in children
B. Marsh, M. White, N. Morton and G. N. C. Kenny

- Disposition of propofol at Caesarean section and in the postpartum period
T. Gin, G. Yau, W. Jong, P. Tan, R. K. W. Leung and K. Chan

- Gastric emptying in pregnancy
A. G. Macfie, A. D. Magides, M. N. Richmond and C. S. Reilly

- Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities
K. R. Davies, A. W. Gelb, P. H. Manninen, D. R. Boughner and D. Bisnaire

- Non-invasive measurement of cardiac output during induction of anaesthesia and tracheal intubation: thiopentone and propofol compared
A. Vohra, A. N. Thomas, N. J. N. Harper and B. J. Pollard

- Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass
F. Boer, J. G. Bovill, P. Ros and H. van Ommen

- Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction
I. H. Lewis, S. J. Pryn, P. I. Reynolds, U. A. Pandit and N. C. T. Wilton

- Preanaesthetic medication with clonidine: a dose-response study
U. A. Carabine, P. M. C. Wright and J. Moore

REVIEW ARTICLES

- Halothane hepatitis
D. C. Ray and G. B. Drummond

- Fibreoptic sensors in clinical measurement
I. H. Yellowlees

RAPID COMMUNICATIONS

- Absorption of isoflurane by silica gel
A. B. Lumb and M. J. Landon

- Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam
K. W. Patterson, P. B. Casey, J. P. Murray, C. A. O'Boyle and A. J. Cunningham

CASE REPORTS

- Extradural haematoma after continuous extradural anaesthesia
I. H. Tekkok, O. Cataltepe, K. Tahta and V. Bertan

- Non-cardiogenic pulmonary oedema after transfusion with granulocyte antibody containing blood: treatment with extracorporeal membrane oxygenation
M. H. Worsley, C. J. Sinclair, C. Campanella, D. C. Kilpatrick and P. L. Yap

APPARATUS

- A system for automatic feedback control of plasma potassium concentration
M. P. D. Heining, R. K. DeBey, S. W. McJames, W. S. Jordan and D. R. Westenskow

CORRESPONDENCE

- Transfer of patients by helicopter
Deep venous thrombosis and anaesthesia
Pharmacokinetics of atracurium
Identification of the interpleural space
Headache after continuous spinal anaesthesia
Midazolam and erythromycin

BOOK REVIEWS

- Regional Anaesthesia in Children
Medical Statistics on Microcomputers
Postanaesthetic Care
Goodman & Gilman's The Pharmacological Basis of Therapeutics

AUGUST

EDITORIAL: Fluid and electrolytes revisited.....	135
<i>S. M. Willatts</i>	

SYMPOSIUM ON FLUID AND ELECTROLYTES

Is postoperative oliguria avoidable?.....	137
<i>P. Sweny</i>	
Management of hyponatraemia	146
<i>J. D. Swales</i>	
Roles of the liver and kidney in acid-base regulation and its disorders	154
<i>R. D. Cohen</i>	
Indications for use of bicarbonate in patients with metabolic acidosis	165
<i>A. I. Arieff</i>	
Calcium for resuscitation?.....	178
<i>E. Erdmann and E. Reuschel-Janetschek</i>	
Fluids for resuscitation	185
<i>J.-L. Vincent</i>	
Potassium in the perioperative period	194
<i>R. S. Vaughan</i>	

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Exeter Meeting, March 22-23, 1991	201P
--	------

CORRESPONDENCE

Relationship between exercise-induced myolysis and malignant hyperthermia	221
Myotonias and susceptibility to malignant hyperthermia	221
29-Gauge spinal needles	222
Tension pneumothorax—wrong tube?	222
Inappropriate heparinization with a cell saver	223
Uncertainties about the ventilatory response to hypoxaemia	223
Regional anaesthesia requires attention to detail	224
Failed tracheal intubation.....	225
Tracheal intubation with the patient in a sitting position.....	225
Analgesia with subhypnotic doses of thiopentone and propofol	226
Incremental spinal anaesthesia and Caesarean section—relevance to the test dose for extradural analgesia	227

BOOK REVIEWS

<i>Advances in Anesthesia</i> , Vol. 7	229
<i>Epidural and Spinal Blockade in Obstetrics</i>	229
<i>Anaesthesia for Ambulatory Surgery</i> , 2nd Edn	229
<i>The Lung—Scientific Foundations</i>	230
<i>Basic Physics and Measurement in Anaesthesia</i> , 3rd Edn.....	230
<i>Gas Monitoring and Pulse Oximetry</i>	230

SEPTEMBER

EDITORIAL: Pain after surgery.....	233
<i>G. Smith</i>	

ORIGINAL ARTICLES

Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac	235
<i>J. W. Burns, H. A. Aitken, R. E. S. Bullingham, C. S. McArdle and G. N. C. Kenny</i>	
Disposition of mepivacaine and bupivacaine enantiomers in sheep	239
<i>L. E. Mather</i>	
Cardiovascular effects and regional clearances of i.v. bupivacaine in sheep: enantiomeric analysis.....	247
<i>A. J. Rutten, L. E. Mather and C. F. McLean</i>	
Inhalation induction of anaesthesia with isoflurane: effect of added carbon dioxide	257
<i>S. A. Coleman, J. W. McGrory, C. J. Vallis and R. J. Boys</i>	
Mental function after general anaesthesia for trans-urethral procedures	262
<i>C. Smith, M. Carter, P. Sebel and P. Yate</i>	
Comparison of sufentanil-nitrous oxide anaesthesia with fentanyl-nitrous oxide anaesthesia in geriatric patients undergoing major abdominal surgery....	269
<i>D. Kietzmann, R. Larsen, J. Rathgeber, M. Bolte and D. Kettler</i>	
Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy	277
<i>L. Knudsen, G. E. Cold, H. O. Holdgaard, U. T. Johansen and S. Jensen</i>	
Pain on injection of propofol: effects of concentration and diluent.....	281
<i>W. Klement and J. O. Arndt</i>	
Comparison of arterial and arterialized venous concentrations of propofol during infusion of propofol	285
<i>R. W. Okell, W. W. Mapleson and M. D. Vickers</i>	
Neuromuscular and clinical effects of mivacurium chloride in healthy adult patients during nitrous oxide-enflurane anaesthesia.....	289
<i>D. R. Goldhill, J. P. Whitehead, R. S. Emmott, A. P. Griffith, B. J. Bracey and P. J. Flynn</i>	
Effects of labetalol on perioperative stress markers and isoflurane requirements	296
<i>D. Amar, H. Shamoon, W. H. Frishman, E. J. Lazar and M. D. Salama</i>	
Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine	302
<i>D. J. Rowbotham, K. Milligan and P. McHugh</i>	
Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms...	306
<i>G. A. Turner, J. P. Newnham, C. Johnson and M. Westmore</i>	
Pharmacokinetics and distribution of ketamine after extradural administration to dogs	310
<i>J. L. Pedraz, M. B. Calvo, A. R. Gascon, R. Hernandez, C. Muriel, L. M. Torres and A. Dominguez-Gil</i>	

RAPID COMMUNICATIONS

- Postoperative myocardial ischaemia in patients with recent myocardial infarction 317
H. Metzler, E. Mahla, B. Rotman, P. Rehak, S. Potisk and W. F. List
- Comparative effects of pipecuronium and tubocurarine on plasma concentrations of histamine in humans 320
M. Naguib, M. Abdulatif and A. Absood
- The loading dose in continuous infusion extradural analgesia in obstetrics 323
E. F. Janes and J. W. McCrory

CASE REPORTS

- Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen 326
M. K. Reeder, M. D. Goldman, L. Loh, A. D. Muir and K. R. Casey
- Controlled hypotension for cerebral aneurysm surgery in the presence of severe aortic coarctation 329
D. B. Goodie and D. L. Rigg
- Compartment syndrome following pressurized infusion 332
M. D. Tobias, C. W. Hanson III, R. B. Heppenstall and S. J. Aukburg
- Backache after extradural anaesthesia in the postpartum period: dissection of thoracic aneurysm .. 335
Y. J. Kao, F. G. Zavisca, J. M. Telles, R. G. Norton and G. B. Racz
- Dilutional hyponatraemia following transurethral operation for clot retention 339
R. G. Hahn

APPARATUS

- AURA: a new respiratory monitor and apnoea alarm for spontaneously breathing patients 341
A. M. Cyna, V. Kulkarni, M. E. Tunstall, J. M. S. Hutchison and J. R. Mallard
- A new optical transducer for arterial pressure measurement 346
C. H. Hackman, P. S. K. Tan, M. K. Chakrabarti and J. G. Whitwam

COMMENTARY

- The first year's experience of an acute pain service . 353
R. G. Wheatley, T. H. Madej, I. J. B. Jackson and D. Hunter

CORRESPONDENCE

- Anaesthetic equipment for a developing country ... 360
 Spinal needles 360
 Opioid receptors—the role of the sigma receptor? .. 361
 Determinants of antagonism of non-depolarizing neuromuscular block 362
 Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide 362

BOOK REVIEWS

- Anaesthesia*, 3rd Edn. 364
A Colour Atlas of Dental Analgesia and Sedation ... 364
ECG Essentials—A Pocket Reference for Systematic Interpretation 364
The Anaesthetic Plan: from Physiologic Principles to Clinical Strategies 365

OCTOBER

- EDITORIALS: I. Silent myocardial ischaemia in preoperative patients: what does it mean and what should be done about it? 367
D. P. de Bono and E. L. Rose
- II. Drug biotransformation by the kidney: how important is it, and how much do we really know? 369
J. W. Sear

ORIGINAL ARTICLES

- Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population ... 373
A. D. Muir, M. K. Reeder, P. Foëx, O. J. M. Ormerod, J. W. Sear and C. Johnston
- Physiological disposition of i.v. morphine in sheep . 378
P. A. Sloan, L. E. Mather, C. F. McLean, A. J. Ritten, R. L. Nation, R. W. Milne, W. B. Runciman and A. A. Somogyi
- Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia 387
Y. Natio, S. Tamai, K. Shingu, R. Fujimori and K. Mori
- Midazolam modifies pancreatic and anterior pituitary hormone secretion during upper abdominal surgery 390
J. P. Desborough, G. M. Hall, G. R. Hart and J. M. Burrin
- Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia 397
L. Delaunay, F. Bonnet and P. Duvaldestin
- A comparison of dexmedetomidine, an α_2 -adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery .. 402
R. Aantaa, M.-L. Jaakola, A. Kallio, J. Kanto, M. Scheinin and J. Vuorinen
- Effects of adenosine triphosphate on the cardiovascular response to tracheal intubation 410
K. Mikawa, N. Maekawa, H. Kaetsu, R. Goto, H. Yaku and H. Obara
- Effects of pindolol on the cardiovascular response to tracheal intubation 416
K. Mikawa, N. Maekawa, R. Goto, H. Kaetsu, M. Hasegawa, M. Yaku and H. Obara

Effect of cisapride on morphine absorption after oral administration of sustained-release morphine	421
<i>D. J. Rowbotham, K. Milligan and P. McHugh</i>	
Gastric emptying and small bowel transit in male volunteers after i.m. ketorolac and morphine.....	426
<i>M. K. Yee, W. D. Evans, P. E. Facey, M. W. J. Hayward and M. Rosen</i>	
Preliminary study to assay plasma amethocaine concentrations after topical application of a new local anaesthetic cream containing amethocaine ..	432
<i>B. Mazumdar, A. A. Tomlinson and G. C. Faulder</i>	
Systemic fentanyl enhances the spread of spinal analgesia produced by lignocaine	437
<i>A. Fassoulaki, C. Sarantopoulos and S. Chondreli</i>	
Effect of P_{aCO_2} on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat	440
<i>W. L. Young, A. I. Barkai, I. Prohovnik, H. Nelson and M. Durkin</i>	
Interaction between betamethasone and vecuronium	447
<i>S. M. Parr, B. J. Robinson, D. Rees and D. C. Galletly</i>	

REVIEW ARTICLE

The prone position for the surgical patient: a historical review of the principles and hazards ...	452
<i>J. M. Anderton</i>	

RAPID COMMUNICATIONS

Effectiveness of preoxygenation in morbidly obese patients	464
<i>M. C. Berthoud, J. B. Peacock and C. S. Reilly</i>	
Metabolic response to colonic surgery: extradural vs continuous spinal.....	467
<i>J. Webster, M. Barnard and F. Carli</i>	
Rapid inhalation induction with isoflurane in humidified carrier gas	470
<i>P. V. van Heerden, D. F. Morrell and P. Becker</i>	

CASE REPORTS

Unsuspected extradural catheterization in an interscalene block	473
<i>L. B. Cook</i>	
Superior sagittal sinus thrombosis after internal jugular vein cannulation	476
<i>P. H. Stephens, G. Lennox, N. Hirsch and D. Miller</i>	
Delayed pneumothorax after subclavian vein catheterization and positive pressure ventilation ..	480
<i>M. C. Cronen, P. W. Cronen, P. Arino and K. Ellis</i>	
Repair of traumatic transection of the thoracic aorta: esmolol for intraoperative control of arterial pressure.....	483
<i>S. G. Fenner, A. Mahoney and J. N. Cashman</i>	

APPARATUS

The pneuPAC hyperbaric variant HB: a ventilator suitable for use within a one-man hyperbaric chamber	488
<i>M. J. Spittal, S. J. Hunter and L. Jones</i>	
Fresh gas utilization of eight circle systems	492
<i>A. M. Zbinden, P. Feigenwinter and M. Hutmacher</i>	

CORRESPONDENCE

Inhalation induction of anaesthesia with isoflurane in children.....	500
Unexpected, difficult laryngoscopy.....	501
Desaturation during total knee replacement	502
Atracurium and suxamethonium	502
Training in fiberoptic laryngoscopy	503
Reporting of deaths	503
Antagonism of benzodiazepine sedation with flumazenil.....	504
Predicting difficult intubation.....	505
Diprivan intensive care sedation in children.....	505
Systolic arterial pressure as a monitor of depth of anaesthesia	506
Pain on i.v. injection	506

BOOK REVIEWS

<i>Trauma Anaesthesia</i>	508
<i>Emergency Drug Therapy</i>	508
<i>Handbook of Obstetric Anaesthesia</i>	509

NOVEMBER

EDITORIALS: I. Resistance to non-depolarizing neuromuscular blocking agents	511
<i>J. M. Hunter</i>	
II. Jaw stiffness—an ill understood condition.....	515
<i>J. M. Sessler</i>	

ORIGINAL ARTICLES

Airway obstruction associated with the use of the Guedel airway	517
<i>A. M. Marsh, J. F. Nunn, S. J. Taylor and C. H. Charlesworth</i>	
Changes in amplitude and latency of the P300 component of the auditory evoked potential with sedative and anaesthetic concentrations of nitrous oxide	524
<i>J. Jessop, D. E. Griffiths, P. Furness, J. G. Jones, D. J. Sapsford and D. A. Breckon</i>	
Effects of i.v. lignocaine on psychological performance and subjective state in healthy volunteers	532
<i>P. J. Armstrong, L. M. Morrison, D. Noble, W. A. Sinclair, B. Tiplady and J. A. W. Wildsmith</i>	
Propofol and midazolam act synergistically in combination.....	539
<i>T. G. Short and P. T. Chui</i>	

Intra-arterial thiopentone is directly toxic to vascular endothelium	546	patient during interscalene brachial plexus block .	621
<i>R. D. MacPherson, L. J. McLeod and A. J. Grove</i>		<i>K. K. Pihlajamäki</i>	
Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor	553	CASE REPORTS	
<i>P. J. D. Andrews, N. M. Dearden and J. D. Miller</i>		Resistance to atracurium in a patient with an increase in plasma alpha ₂ globulins	623
Ketamine for caudal analgesia in children: comparison with caudal bupivacaine	559	<i>A. J. Tatman, S. R. Wrigley and R. M. Jones</i>	
<i>M. Naguib, A. M. Y. Sharif, M. Seraj, M. El Gammal and A. A. Dawlatly</i>		Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia	626
Maternal temperature regulation during extradural analgesia for labour	565	<i>M. K. Reeder, A. D. Muir, P. Foëx, M. D. Goldman, L. Loh and D. Smart</i>	
<i>W. R. Camann, L. A. Horvath, N. Hughes, A. M. Bader and S. Datta</i>		Unusual presentation of acute upper airway obstruction caused by an anterior mediastinal mass	632
Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration ...	569	<i>T. M. Akhtar, S. Ridley and C. J. Best</i>	
<i>E. S. Shearer, E. P. O'Sullivan and J. M. Hunter</i>		Transient ischaemic attack after spinal anaesthesia ..	635
Intraoperative assessment of atracurium-induced neuromuscular block using double burst stimulation	574	<i>R. A. Chung and A. M. Goodwin</i>	
<i>N. Braude, H. A. L. Vyvyan and M. J. Jordan</i>		APPARATUS	
Alcohol after sedation with i.v. midazolam-fentanyl: effects on psychomotor functioning	579	Temperature dependence of LED and its theoretical effect on pulse oximetry	638
<i>J. L. Lichtor, J. Zacry, J. L. Apfelbaum, B. S. Lane, G. Rupani, R. A. Thisted, C. Dohrn and K. Korttila</i>		<i>K. J. Reynolds, J. P. de Kock, L. Tarassenko and J. T. B. Moyle</i>	
Clinical and haemodynamic effects of milrinone in the treatment of low cardiac output after cardiac surgery	585	ABSTRACTS	
<i>E. M. Wright and K. M. Sherry</i>		Proceedings of the Anaesthetic Research Society, Manchester Meeting, July 12-13, 1991	644P
Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine	591	CORRESPONDENCE	
<i>R. Wenstone, J. M. Campbell, P. D. Booker and R. McKay</i>		Spinal anaesthesia in obstetrics	663
Influence of hypertonic volume replacement on the microcirculation in cardiac surgery	595	Fresh gas requirement of the Bain system	663
<i>J. Boldt, B. Zickmann, C. Herold, M. Ballesteros, F. Dapper and G. Hempelmann</i>		Picolax bowel preparation	664
Relationship between analgesia and respiratory depression for mu opioid receptor agonists in mice	603	Interference with pacemaker function	664
<i>D. G. Stott and B. J. Pleury</i>		Anaesthesia and bone marrow aplasia	665
Modification by drugs used in anaesthesia of CNS stimulation induced in mice by laudanosine and strychnine	608	Bacterial growth in propofol	665
<i>W. M. Al-Muhandis, G. R. Lauretti and B. J. Pleury</i>		Speed of onset of analgesia of diamorphine or morphine	666
Determination of contamination of a chemical warfare-proof operating theatre with volatile anaesthetic agents and assessment of anaesthetic gas scavenging systems	614	First use of combined spinal-extradural anaesthesia	666
<i>S. Yoganathan, I. G. Johnston, C. J. Parnell, I. T. Houghton and J. Restall</i>		BOOK REVIEWS	
RAPID COMMUNICATIONS		<i>Regional Anaesthesia</i> , 2nd Edn.	668
Haemodynamic effects of propofol: induction with 2.5 mg kg ⁻¹	618	<i>Ambulatory Anaesthesia and Sedation, Impairment and Recovery</i>	668
<i>J. E. Fairfield, A. Dritsas and R. J. Beale</i>		<i>Intraoperative Use of Echocardiography</i>	668
Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the		<i>A Pocket Book of Intensive Care: Data, Drugs and procedures</i> , 2nd Edn	669
		DECEMBER	
		EDITORIALS: I. Assessment of the placental circulation	671
		<i>J. Moore</i>	
		II. Headache after spinal anaesthesia	674
		<i>J. A. Reid and J. Thorburn</i>	
		ORIGINAL ARTICLES	
		Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation	678
		<i>S. Alahuta, J. Räsänen, R. Jouppila, P. Jouppila and A. I. Hollmén</i>	

Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the feto-placental unit during elective Caesarean section	683	Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick.....	764
<i>A. J. McLintic, F. H. Danskin, J. A. Reid and J. Thorburn</i>		<i>C. McLoughlin, R. K. Mirakhor, E. R. Trimble and R. S. J. Clarke</i>	
Use of a 25-gauge Whitacre needle to reduce the incidence of postdural puncture headache.....	690	Comparison of contemporaneous and retrospective assessment of postoperative pain using the visual analogue scale.....	768
<i>J. Lynch, I. Krings-Ernst, K. Strick, K. Topalidis, H. Schaaf and M. Fiebig</i>		<i>W. D. H. Liu and A. R. Aitkenhead</i>	
Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients	694	REVIEW ARTICLE	
<i>N. E. Sharrock, G. Go and R. Mineo</i>		Anaesthesia for patients with transplanted hearts and lungs undergoing non-cardiac surgery	772
Comparison of plain and alkalinized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural Caesarean section.....	699	<i>I. H. Shaw, A. J. B. Kirk and I. D. Conacher</i>	
<i>R. Fernando and H. M. Jones</i>		RAPID COMMUNICATIONS	
Patterns of oxygenation after thoracotomy.....	704	P6 acupuncture and postoperative vomiting after tonsillectomy in children	779
<i>M. D. Entwistle, P. G. Roe, D. J. Sapsford, R. G. Berrisford and J. G. Jones</i>		<i>S. M. Yentis and B. Bissonnette</i>	
Rib cage contribution to resting and carbon dioxide stimulated ventilation during 1 MAC isoflurane anaesthesia	712	Dose requirements of atracurium in paediatric intensive care patients.....	781
<i>A. B. Lumb, A. J. Petros and J. F. Lunn</i>		<i>O. T. Kushimo, M. J. Darowski, P. Morris, S. Hollis and G. Meakin</i>	
Screening for antibodies associated with halothane hepatitis	722	CASE REPORT	
<i>K. L. Hastings, C. Thomas, A. K. Hubbard and A. J. Gandolfi</i>		Management of labour and delivery in patients with intracranial neoplasms	784
Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic ...	729	<i>S. R. Finfer</i>	
<i>F. Carli, J. Webster, M. Pearson, J. Pearson, S. Bartlett, P. Bannister and D. Halliday</i>		APPARATUS	
Effects of low concentrations of cyclopropane and halothane on peak velocity of saccadic eye movements	735	Non-invasive measurement of cardiac output by thoracic electrical bioimpedance: a study of reproducibility and comparison with thermodilution...	788
<i>J. Yoshizumi, R. W. Marshall and M. D. Vickers</i>		<i>C. Jewkes, J. W. Sear, F. Verhoeff, D. J. Sanders and P. Foëx</i>	
Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section.....	741	Pressure support ventilation using a new tracheal gas injection tube	795
<i>W. B. Ashton, M. F. M. James, P. Janicki and P. C. Uys</i>		<i>L. Beydon, D. Isabey, G. Boussignac, F. Bonnet, P. Duvaldestin and A. Harf</i>	
Effect of sublingual buprenorphine on gastric emptying of a liquid meal	748	COMMENTARY	
<i>T. N. Trotter, D. J. Rowbotham, I. Windram and M. C. Mushambi</i>		Guest Reviewers for 1991	801
General anaesthetics induce only histamine release selectively from human mast cells.....	751	CORRESPONDENCE	
<i>C. Stellato, V. Casolaro, A. Ciccarelli, P. Mastronardi, B. Mazzarella and G. Marone</i>		Venous sequelae after i.v. diclofenac	803
First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model.....	759	Intra-arterial regional analgesia	803
<i>M. G. A. Palazzo, E. A. Kalso, E. Argiras, R. Madgwick and J. W. Sear</i>		Tracheal intubation with the patient in the sitting position	804
		BOOK REVIEW	
		<i>Towards a New Pharmacotherapy of Pain.....</i>	805
		Index to Volume 67.....	807

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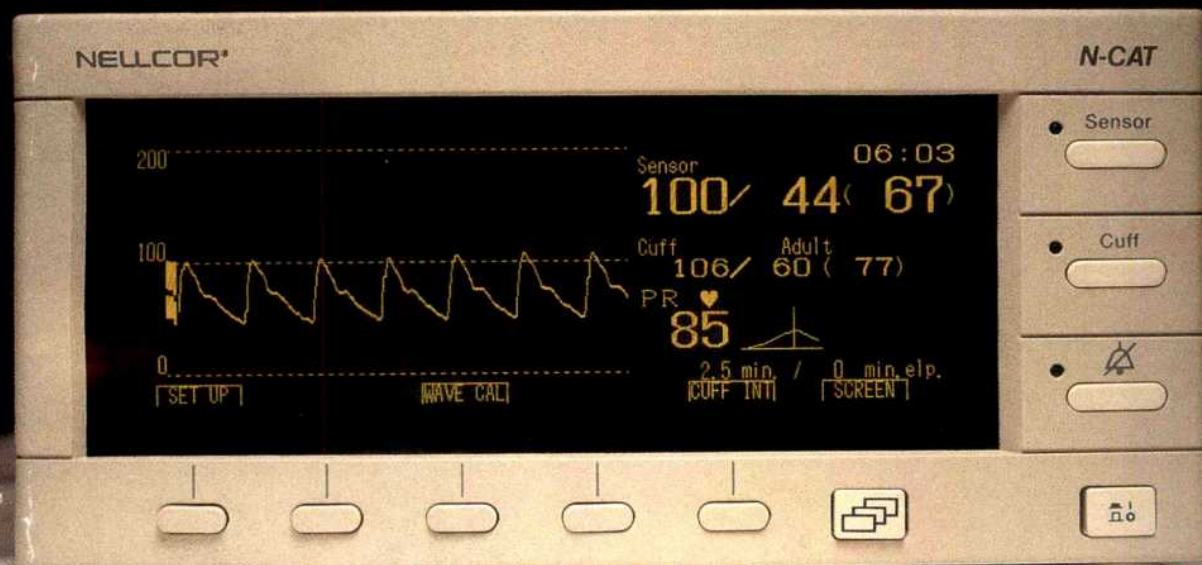
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CONTENTS

	PAGE		PAGE
EDITORIALS: I. Assessment of the placental circulation	671	First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model	759
J. Moore		M. G. A. Palazzo, E. A. Kalso, E. Argiras, R. Madgwick and J. Sear	
II. Headache after spinal anaesthesia	674	Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick	764
J. A. Reid and J. Thorburn		C. McLoughlin, R. K. Mirakhur, E. R. Trimble and R. S. J. Clarke	
ORIGINAL ARTICLES		Comparison of contemporaneous and retrospective assessment of postoperative pain using the visual analogue scale	768
Effects of extradural bupivacaine with adrenaline for Caesarean section on uteroplacental and fetal circulation	678	W. D. H. Liu and A. R. Aitkenhead	
S. Alahuta, J. Räsänen, R. Jouppila, P. Jouppila and A. I. Hollmén		REVIEW ARTICLE	
Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the feto-placental unit during elective Caesarean section	683	Anaesthesia for patients with transplanted hearts and lungs undergoing non-cardiac surgery	772
A. J. McLintic, F. H. Danskin, J. A. Reid and J. Thorburn		I. H. Shaw, A. J. B. Kirk and I. D. Conacher	
Use of a 25-gauge Whitacre needle to reduce the incidence of postdural puncture headache	690	RAPID COMMUNICATIONS	
J. Lynch, I. Krings-Ernst, K. Strick, K. Topalidis, H. Schaaf and M. Fiebig		P6 acupuncture and postoperative vomiting after tonsillectomy in children	779
Effect of i.v. low-dose adrenaline and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar extradural anaesthesia in elderly patients	694	S. M. Ventis and B. Bissonnette	
N. E. Sharrock, G. Go and R. Mineo		Dose requirements of atracurium in paediatric intensive care patients	781
Comparison of plain and alkalized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural Caesarean section	699	O. T. Kushimo, M. J. Darowski, P. Morris, S. Hollis and G. Meakin	
R. Fernando and H. M. Jones		CASE REPORTS	
Patterns of oxygenation after thoracotomy	704	Management of labour and delivery in patients with intracranial neoplasms	784
M. D. Entwistle, P. G. Roe, D. J. Sapsford, R. G. Berrisford and J. G. Jones		S. R. Finfer	
Rib cage contribution to resting and carbon dioxide stimulated ventilation during 1 MAC isoflurane anaesthesia	712	APPARATUS	
A. B. Lumb, A. J. Petros and J. F. Lunn		Non-invasive measurement of cardiac output by thoracic electrical bioimpedance: a study of reproducibility and comparison with thermodilution	788
Screening for antibodies associated with halothane hepatitis	722	C. Jewkes, J. W. Sear, F. Verhoeff, D. J. Sanders and P. Foëx	
K. L. Hastings, C. Thomas, A. K. Hubbard and A. J. Gandolfi		Pressure support ventilation using a new gas injection tube	795
Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic	729	L. Beydon, D. Isabey, G. Boussignac, F. Bonnet, P. Duvaldestin and A. Harf	
F. Carli, J. Webster, M. Pearson, S. Bartlett, P. Bannister and D. Halliday		COMMENTARY	
Effects of low concentrations of cyclopropane and halothane on peak velocity of saccadic eye movements	735	Guest Reviewers for 1991	801
J. Yoshizumi, R. W. Marshall and M. D. Vickers		CORRESPONDENCE	
Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section	741	Venous sequelae after i.v. diclofenac	803
W. B. Ashton, M. E. M. James, P. Janicki and P. C. Uys		Intra-arterial regional analgesia	803
Effect of sublingual buprenorphine on gastric emptying of a liquid meal	748	Tracheal intubation with the patient in the sitting position	804
T. N. Trotter, D. J. Rowbotham, I. Windram and M. C. Mushambi		BOOK REVIEW	
General anaesthetics induce only histamine release selectively from human mast cells	751	Towards a New Pharmacotherapy of Pain	805
C. Stellato, V. Casolaro, A. Ciccarelli, P. Mastrorardi, B. Mazzarella and G. Marone		Index to Volume 67	807